Division of Cancer Prevention (DCP)

Study Site Monitoring Manual

August 2002

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1. INTRODUCTION

1.1 Purpose of Site Monitoring

Clinical trials site monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements. The FDA requires that clinical investigations involving human subjects be periodically monitored (312.56 Review of Ongoing Investigations). In order to fulfill this regulatory requirement, the Division of Cancer Prevention (DCP) representative, which is the Westat Team, periodically visits the site to verify that:

- The rights and well-being of human subjects are protected;
- The study data are of the highest quality and integrity; and
- The study is in compliance with the currently approved protocol/amendments, GCP, and other regulatory requirements.

1.2 Purpose of this Manual

DCP created the Clinical Trials *Site Monitoring Manual* to provide clinical study site staff conducting DCP studies with reference information about monitoring clinical research studies.

The user of this manual should have a basic understanding of the clinical research process. The manual does not replace protocol-specific instructions or procedures. This manual will be merged into a comprehensive Clinical Trials Resource, which will be on the DCP website and will be updated regularly.

The manual provides general information about DCP's mission and organization. Study staff roles and responsibilities are described. Participant enrollment and study record maintenance are outlined. Serious Adverse Events (SAEs), protocol deviations, and participant status changes are reviewed. The content of the various types of monitoring visits are delineated as well as the process for conducting the visits. A list of staff, key to the management of clinical trials, is provided as well as a Glossary of Terms.

1.2.1 Manual Feedback

Feedback about the manual content and organization can be directed to Erin Iturriaga at Eriniturriaga@westat.com.

2. DCP ORGANIZATIONAL OVERVIEW, DESCRIPTION OF PREVENTION TRIALS, AND SUMMARY OF CONTRACTOR RESPONSIBILITIES

2.1 Overview

The goal of the National Cancer Institute (NCI) is to stimulate and support scientific discovery and its application to achieve a future where all cancers are uncommon and easily treated. NCI is leading the world in defining the standard of cancer care and prevention. The agency has six divisions each specializing in a different aspect of cancer research. The Division of Cancer Prevention (DCP) is one such division within NCI. The vision of DCP is:

> *"A growing, dynamic matrix organization committed to evidence-based cancer prevention research. The goals are to advance biomedical science, strengthen preventive medicine, and improve public health. Research is carried out through the positive interactive efforts of all DCP staff dedicated to the success of the Division's activities."*

2.2 Prevention Trials

Because the process of carcinogenesis can take decades to manifest itself, it also provides time and opportunity to intervene to stop or reverse its progress before the clinical appearance of cancer. Prevention trials study ways to reduce the risk, or chance, of developing cancer. These trials can study healthy people who have not previously had cancer, or people who have had cancer and are trying either to reduce the chance of developing a new type of cancer, or prevent a reoccurrence of the original cancer.

Prevention trials generally take one of two forms. *Action studies* (doing something) focus on finding out whether actions people take, such as exercising more or quitting smoking, can prevent cancer. *Agent studies* (taking something in) focus on examining whether taking certain medicines, vitamins, minerals, or food supplements (or a combination of them) can prevent cancer. There are three types of trials: screening trials, control trials, and chemoprevention trials.

- **Screening Trials:** The goal of screening trials is to develop tools for detecting cancer before an individual becomes symptomatic. Various screening techniques are

evaluated to see if early detection and treatment of disease improves the outcome. Screening can include:

- Imaging tests that produce images of organs and tissues in the body;
- Biological tests that take samples such as blood, urine, and other bodily fluids and tissues; and
- Genetic tests which look at biomarkers.

- **Control Trials:** A cancer-control trial assesses the effect of an intervention on cancer symptoms, side effects of treatment, or the participant's quality of life. As with other clinical trials supported by DCP, the intervention can be pharmaceutical, nutriceutical, dietary, or behavioral.

- **Chemoprevention Trials:** Chemoprevention trials may be Phase I, Phase II, or Phase III studies.

  - Phase I chemoprevention trials are the first studies in people which evaluate how new agents should be given (by mouth, injected into the blood, or injected into the muscle), how often, and what dose is safe. A Phase I trial usually enrolls only a small number of patients, sometimes as few as a dozen. DCP also administers a pre-clinical program (Rapid Access to Prevention Intervention Development Program) to foster cancer prevention agent development and move promising agents into early clinical trials.
  - Phase II chemoprevention trials are conducted in larger groups of participants who are at high risk for certain cancers. These continue to test the safety of the drug and begin to evaluate how well the new drug works. Phase II studies usually focus on a particular type of cancer.
  - Phase III chemoprevention trials are conducted either in populations at high risk for specific cancers or in participants from the general population. These studies test new agents, a combination of agents, or a new surgical procedure in comparison to the current standard. A participant will usually be assigned to the standard group or the investigational group at random (in a systematic process called randomizations). Phase III trials often enroll large numbers of participants and may be conducted at a physician's office, clinic, hospital, or cancer center nationwide.

2.3 DCP Organization

Peter Greenwald, M.D. is the Director of the Division of Cancer Prevention, and Leslie Ford, M.D. is the Acting Deputy Director and Associate Director for Clinical Research. DCP is organized with seven Foundations of Prevention Research Groups and four Organ System Research Groups. The

Protocol Information Office (PIO) is the coordinating office for Cancer Prevention Studies. Linda Parreco, R.N., M.S. is the head of the PIO. All protocol activity from protocol development to final report submission is coordinated through that office. The PIO works closely with the Organ System Groups, Chemopreventive Agent Development Research Group (CADRG), and Community Oncology and Prevention Trials (COPTRG) to facilitate the research process for Principal Investigators conducting cancer prevention trials. The DCP Matrix Organizational Chart, Figure 2-1 on page 2-5, displays the organization of the division. A list of names, addresses, and telephone numbers critical to DCP clinical trials management are in Appendix A.

2.4 Prevention Protocol Management

There are three primary areas of protocol management:

- Protocol Development;
- Regulatory Affairs; and
- Study Site Monitoring.

DCP has enlisted the support of several contractors to assist with these endeavors. CCS Associates in Mountain View, California assists with protocol development and regulatory affairs and the Westat Team manages the study site monitoring, data management, and informatics activities.

The CCS Associates contractor is responsible for assisting the PIO, Organ Research Group personnel, and study site staff with protocol development and management of regulatory issues during the conduct of the study. CCS Associates provides technical assistance with drafting, revising, and managing drug data files, IND packages, and New Drug Application (NDA) documents for which DCP is the sponsor. Regulatory documents will be described in Chapter 5, Study Record Maintenance.

The Westat Team consists of staff with clinical trials monitoring experience, clinical trials data management experience, and clinical trials database informatics/experience. Over the next 5 years, the Westat Team will:

- Transition clinical data management from paper forms to electronic systems (effective with contracts awarded in 2003);

- Enhance existing DCP Enterprise System Knowledgebase (DESK) and software applications to collect, analyze, and report the study data by creating a central data repository;
- Standardize site monitoring processes; and
- Provide consistent education and training to site staff about the conduct and management of clinical research trials.

A glossary of terms in Appendix B is provided to assist with definitions of DCP prevention terminology.

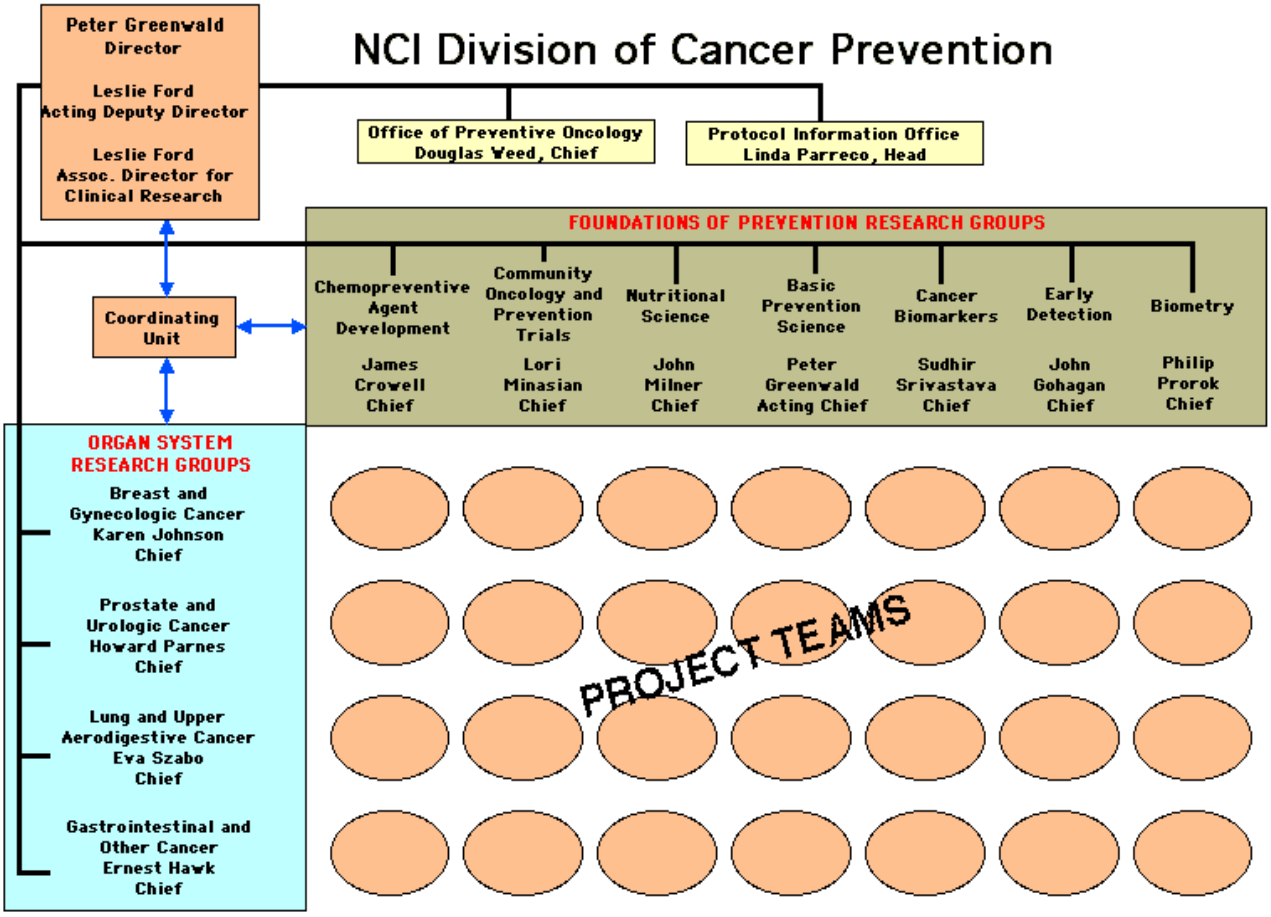

Figure 2-1. DCP Matrix Organizational Chart

3. DCP STUDY STAFF ROLES AND RESPONSIBILITIES

Members of the study site research team usually include at least one of the following: Principal Investigator, study coordinator or research nurse, and pharmacist. Members of the research team at DCP include the Medical Monitor, Organ System Group nurse specialist, PIO staff, and Contract Officer. Each member of the research team has roles and responsibilities defined by the Code of Federal Regulations, and the International Conference on Harmonisation Guidelines for Good Clinical Practice. DCP adheres to these regulations and guidelines.

The National Institutes of Health (NIH) mandates education on human subject participation for all investigators and research team members who apply for or receive NIH funds for research involving people. Each research team member must document completion of training in human subjects protection and this documentation must be maintained at the site. An online continuing education program has been developed by the National Cancer Institute to fulfill this requirement. The Human Participants Protection Education for Research Teams course is available online at the following website: http://cme.nci.nih.gov.

The following sections describe the roles of various research team members and tasks that are often performed by them or delegated to them. Though select tasks are delegated to the study coordinator, research nurse, or pharmacist, the Principal Investigator is ultimately responsible for the research conducted at the site.

3.1 Principal Investigator

The Principal Investigator (PI) is responsible for the overall conduct of research activities at the site. The PI is expected to comply with the Code of Federal Regulations (CFR) and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH/GCP). By signing the Form FDA 1572, the PI agrees to:

- Conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- Personally conduct or supervise the described investigation(s).

- Inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

- Report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CRF 312.64.

- Read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

- Ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

- Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

- Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

- Make no changes in the research without IRB approval except where necessary to eliminate apparent immediate hazards to human subjects.

- Agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

NOTE: Refer to Section 9 of the Form FDA 1572 for complete information on investigator responsibilities. The instructions for completing the form are located at this link: http://www.fda.gov/cder/forms/1571-1572-help.html. The Form FDA 1572 can be found at http://forms.psc.gov/forms/FDA/fda.html or see Appendix C for a sample of the form.

3.2 Study Coordinator or Research Nurse

A well-implemented protocol is often attributable to an organized, responsible study coordinator or research nurse. The PI may delegate some or all of the following tasks to the study coordinator or research nurse. Under the PI's guidance, this person may:

- Prepare regulatory documentation (IRB approval, IRB-approved informed consent, additional certifications defined in the protocol, etc.) required for protocol-specific site registration for submission to the PIO.
- Ensure the study is conducted in compliance with protocol requirements.
- Maintain IRB correspondence and regulatory documentation.
- Recruit potentially eligible participants for clinical trials enrollment.
- Meet with the study participant to review the details of study enrollment.
- Evaluate study participant for protocol eligibility.
- Ensure that informed consent has been obtained from the participants before initiating research-related activities.
- Develop strategies to retain study participants on clinical trial.
- Schedule tests and appointments for participants within timeframes required by protocol.
- Validate participant height and weight for accurate body surface area determination.
- Send the prescriptions for study medication to the pharmacist.
- Complete Case Report Forms (CRFs) accurately, and retain a copy in the CRF Notebook.
- Maintain source documentation for each study participant in accordance with the protocol.
- Instruct and educate participants regarding study treatment modalities and anticipated side effects and their management.
- Provide guidance to the Principal Investigator, pharmacist, and participant on dose adjustment based on protocol dose modification section.
- Inform the pharmacist about any dose changes.
- Collect returned study medication and monitor participant dosing compliance.

- Identify abnormal laboratory results and obtain repeat evaluations as required by the protocol.
- Identify and document adverse events and serious adverse events.
- Initiate Serious Adverse Experience Reports (SAEs) and obtain the PI's signature within the proper timeframes, notify proper individuals stated in the protocol, and fax report to DCP.
- Submit protocol and amendments, protocol submission worksheet, and case report forms to the DCP PIO for Review.
- Identify and document protocol deviations.
- Respond to data queries in a timely manner.
- Contact DCP organ system research nurse with questions regarding study implementation.
- Update PI on study status.

NOTE: The PI is responsible for the research conducted at the site, even if select tasks are delegated to the study coordinator, research nurse, or pharmacist.

3.3 Pharmacist

The pharmacist or designated qualified staff member is accountable for:

- Study drug supply, storage, preparation, dispensation, and disposal;
- Accountability records and record security;

  Retain:

  1. Instructions for ordering study drug;
  2. Shipping receipts and return records;
  3. NCI Drug Accountability Record Forms (DARFs); and
  4. Transfer Forms.
- Medication administration record;
- Maintenance of blinded study integrity; and

- Instruction to the care provider on the proper method of drug administration.

NOTE: The PI is responsible for the research conducted at the site, even if select tasks are delegated to the CRA, research nurse, or pharmacist.

3.4 DCP Medical Monitor

The Medical Monitor is a physician who is a member of the DCP staff. She or he belongs to one of the Organ System Research Groups or one of the Foundations of Prevention Research Groups. The Medical Monitor's responsibilities include:

- Managing scientific portfolios of grants, contracts, and other long-term projects in a distinct area of cancer prevention science;
- Ensuring the quality and scientific integrity of protocol design, implementation, and data;
- Reviewing protocols;
- Reviewing Serious Adverse Events Reports and Deviations;
- Participating in the development of work statements; and
- Serving as a resource to study PIs and site staff for protocol-specific clarification.

3.5 Organ System Group Nurse Specialist

The Organ System Group nurse specialist is a registered nurse with advanced knowledge in the conduct of clinical research studies. The nurse specialist responsibilities include:

- Serving as a resource to site staff conducting cancer prevention research;
- Participating in the management of cancer prevention research protocols as requested by the medical monitor;
- Participating in DCP project teams and work groups; and
- Update PI on study status.

3.6 Contract Officer

The Contract Officer is a staff member of DCP responsible for the performance of complex pre-award and post-award contracting functions. The Contract Officer is the human representative, authorized by the United States to enter into contracts (i.e. commit federal funds) and administer them. The Contract Officer's acts are binding. The Contract Officer's responsibilities include:

- Providing guidance and technical assistance to program personnel who are involved in the planning and development of specifications, descriptions, and statements of work;
- Reviewing and evaluating requests for acquisitions, analyzing requirements, and determining adequacy and completeness of requests; recommending and/or making revisions;
- Recommending or deciding on the types of contracts;
- Coordinating the establishment of a peer review of proposals;
- Analyzing proposals, evaluating technical, cost/price data, and other factors, and determining reasonableness; and
- Working with DCP officials to develop negotiation strategies.

3.7 Clinical Research Associate

The Clinical Research Associate (CRA) is an appropriately qualified Westat Team Member, by training and experience, who is responsible for ensuring that clinical trials are conducted according to the Code of Federal Regulations and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The CRA represents DCP in the monitoring process. The CRA is responsible for verifying/assuring:

- The acceptability and accuracy of the Investigator and site's qualifications;
- The acceptability of the agent storage facilities;
- Adequacy of clinical supplies;
- The initial and ongoing acceptability of the investigation site facilities;
- The investigational agents are supplied only to subjects who are eligible to receive them, and according to the dosing specified in the protocol;

- Participants are given the necessary instructions on properly using, handling, storing, and returning the study agent;
- The receipt, use, and returns of the investigational agents at the sites are controlled and documented accurately;
- The appropriate disposition of unused clinical trial supplies;
- The study site research team complies with the protocol, applicable regulatory requirements, and GCPs;
- Informed consent was obtained prior to each participant's participation in the trial;
- Study site staff are adequately informed and receive all trial documents and supplies to enable them to properly conduct the trial;
- The Principal Investigator has appropriately delegated his/her authority;
- The Principal Investigator is enrolling only eligible subjects;
- Accurate reporting of the participant's enrollment rate;
- Accurate, complete and current source documents and trial records are maintained;
- The Principal Investigator provides all the required reports, notifications, applications, and IRB submissions, and that these documents are accurate, complete, timely, legible, and dated;
- The accuracy and completeness of the Case Report Form (CRF) relative to the source information;
- Appropriate reporting of adverse events (AEs) and Serious Adverse Events (SAEs);
- Protocol changes/deviations are documented and reported to DCP and Institutional Review Board (IRB); and
- Significant protocol deviations are reported to the Investigator, with appropriate action taken to prevent the recurrence of the detected deviations.

4. PARTICIPANT ENROLLMENT

4.1 Initiation of New Study

Prior to initiating a new study, the following approvals and materials must be obtained or in process and the appropriate site staff should also be well-prepared to facilitate each of the following:

- IRB approval granted and letter/documentation sent to DCP;
- Executable contract with the lead organization;
- Study agent supply onsite;
- Case Report Forms present and available for use;
- Initiation site visit with Westat CRA, DCP staff and involved study site staff;
- Copies of the IRB/DCP-approved informed consent forms and recruitment materials available for the research team to provide to potential participants;
- Procedures for collection, shipping, and processing of laboratory specimens prepared;
- Determine the population that is appropriate for the study; and
- Patient Identification (PID) logbook and screening log onsite.

4.2 The Enrollment Process

Once the initiation visit has taken place and the site is prepared logistically to conduct the study, the enrollment process may begin (see Figure 4-1). Enrollment refers to the tasks that each site undertakes to initiate participant accrual beginning with recruitment and then a review of potentially eligible participants.

4.2.1 Participant Recruitment

Recruitment for DCP chemoprevention trials will occur in different ways depending upon the particular study, research site, and creativity of assigned recruitment staff. Some participants may be

recruited through primary care practices and specialty practices such as dermatology or urology. Other participants may be accessed through oncology clinics. General media or specific outreach methods can be utilized to recruit members of the public. Each site is responsible for developing a recruitment plan, recruitment materials, and methods to retain study participants. All participant recruitment materials must be IRB-approved prior to use.

Participant Enrollment Process

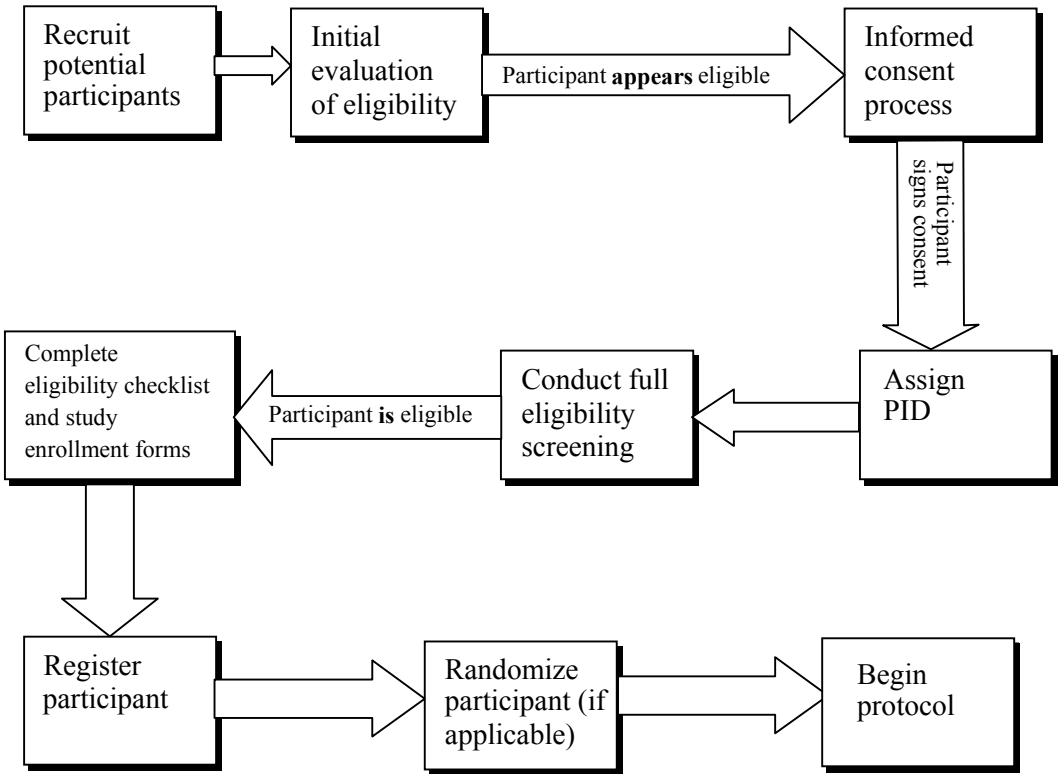

Figure 4-1. Participant Enrollment Process

It is helpful for site study staff to recognize why people decide to participate in cancer chemoprevention clinical trials and recognize some of their reservations. Potential participants may want to take a more active role in their health care and/or receive regular medical attention, or they may simply want to assist in the gathering of medical knowledge. On the other hand, they may worry about perceived and/or real side effects, payment issues, and being viewed as "guinea pigs." The process of informed consent about clinical research participation starts with the recruitment phase of a study.

4.2.2 Initial Evaluation of Participant's Eligibility Using the Inclusion/Exclusion Criteria

A general assessment of the participant's potential eligibility should be made to determine if further screening is warranted. All study sites are expected to comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Tests and procedures to confirm eligibility can only be done once the participant has signed the informed consent.

4.2.3 Obtaining Informed Consent

Every effort must be made to protect the rights of the study participants. An investigator may not involve a participant in research (including tests to evaluate eligibility) unless the investigator or his/her representative has obtained the legally recognized IRB-approved informed consent form of the participant. An investigator should ask for such informed consent only under circumstances that provide the prospective participant sufficient opportunity to consider whether or not to participate.

NOTE: Participants who are minors or who cannot make their own health care decisions will need a legal representative to provide consent.

Obtaining informed consent is more than obtaining a signature on a form. It is a process designed to:

- Provide the participant with current and ongoing information about the study;
- Ensure the participant understands the information that has been presented and has an opportunity to ask questions;
- Discuss the participant's rights as outlined in the consent form;
- Allow the participant the opportunity to agree or disagree to take part in the study; and
- Allow the participant the opportunity to freely withdraw from the study in the future.

NOTE: During a site monitoring visit, the Westat Clinical Research Associate (CRA) will check the date the participant or legal representative signed the informed consent, and whether that signature was obtained on or before the date(s) that any screening or other study-related procedures were conducted.

The CRA will also review the date an informed consent form was approved by the IRB and will determine whether a participant's signature was obtained after IRB approval.

4.3 Assigning a Participant Identification Number (PID)

Once a participant has been identified as potentially eligible for enrollment in the study, and pre-entry clinical/laboratory evaluations have been scheduled, the participant will be assigned a PID. Each clinical study site will develop its own PID system. One example of a system would be to use a participant's initials plus a unique four or five digit number. Once a participant has been assigned a PID number, that number never changes. If the participant is enrolled in future stages of the study, he/she will retain that PID number. If the subject does not enroll, that PID number will not be reassigned. The PID logbook that contains both participants' names and PID numbers must be kept in a locked, secure place.

NOTE: DCP will comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in order to protect the privacy of research participants. This rule continues to be reviewed and revised. It is anticipated to become effective in April 2003. This rule states that initials and full birth date are identifying information. Therefore, any participant-related materials that will be seen outside of the research site (i.e., investigator progress reports or SAE reports) should include only the PID number, year of birth, gender, and race.

4.4 Determining Eligibility

Once a participant is identified as a potential candidate for a study and the informed consent for the protocol is obtained, the screening (or pre-entry or pre-treatment) to fully evaluate and confirm eligibility begins. This eligibility evaluation may include laboratory and/or clinical tests. The results of the tests determine whether the participant satisfies the inclusion/exclusion criteria of the protocol. All screening evaluations are performed prior to the participant's registration.

All participants that undergo screening for a study must be recorded in a study-specific screening log. If a participant is found to be ineligible or otherwise does not enroll in the study, the reason for this must be stated in the log.

Persons who provided informed consent, but who are not eligible for the study due to the inclusion or exclusion criteria, must be told why they cannot participate in the clinical trials. This is often done by the research nurse or study coordinator. The reason(s) for ineligibility must be recorded in the participant's study chart and should include a note indicating the understanding by the participant.

After the eligibility evaluation is complete, use the protocol-specific Eligibility Checklist (a type of CRF) to document that the participant fulfills the inclusion/exclusion criteria of the protocol. If the participant is eligible for the protocol, complete the study enrollment form (another CRF) and the participant is ready for registration.

NOTE: During a site monitoring visit, the Westat CRA will check the Eligibility Checklist CRF against the source documentation. The CRA may also ask to review the screening log.

4.5 Registering/Randomizing Participant

The mechanism for officially registering and randomizing participants onto a DCP study will vary depending upon the protocol. The person responsible for randomizing participants also will differ with each protocol. For example, if a pharmaceutical company is involved in the study and is charged with randomization responsibilities, site staff may be required to call or fax the eligibility and enrollment forms to that company. In other instances, the research pharmacist at the site may be responsible for randomization. DCP does not have a central mechanism for registering and randomizing participants. Therefore, it is critical that site staff only enter eligible participants on study, as eligibility may be checked only at the time of the annual site monitor visit. During site monitoring visits, participant eligibility will be one of the main items assessed by the Westat CRA.

5. STUDY RECORD MAINTENANCE

One of the primary responsibilities of the Westat Clinical Research Associate (CRA) during a site visit is to review the study records and ensure that they are complete and accurate. This chapter describes the different types of study records and what the Westat CRA will review during a site visit.

5.1 Regulatory Binder

The Regulatory Binder contains all study-specific information and regulatory documentation. The Binder does not include completed Patient Case Report Forms (CRFs) or signed patient informed consent forms. The Study Binder, Investigator Binder, Administrative Binder, Regulatory Files, and Investigator's Study Files are terms used synonymously to describe the Regulatory Binder. The Regulatory Binder may take the form of file folders, a 3-ring binder, a filing system, or a combination of these organizational methods. The site keeps all original informed consents that have been signed by participants. It is recommended these be maintained in a separate binder.

Typically the Regulatory Binder contains the elements described in the Regulatory Binder Checklist. The order and organization of the documents may vary from site to site. During a site visit, the CRA will expect to review the regulatory binder to ensure its completeness.

5.1.1 Regulatory Binder Checklist

The following documents should be found in the Regulatory Binder, though the order may vary by site:

- ☐ Protocol and Amendments (all versions)
- ☐ Investigator brochure (all versions)
- ☐ Case Report Forms (a blank set of CRFs that can be duplicated)
- ☐ Current Form FDA 1572s

☐ Curricula vitaes (CVs) and documentation of professional licensure of all investigators

☐ Financial Disclosure Forms for anyone on the 1572s

☐ IRB approval documentation for:

- The protocol;
- Protocol amendments;
- Original informed consent form;
- Other written (educational) materials provided to the subjects;
- Amended versions of the consent form;
- Continuation of the study (based on annual or periodic reviews); and
- Study advertising.

☐ IRB Correspondence

- Notification of new safety information and the IRB's recommendations pertaining to this information; and
- IRB roster and credentials of IRB members.

☐ Informed Consent

- Original copies of IRB-approved versions

NOTE: Original signed patient informed consents are usually kept in the patient's medical records or research records, and not in the Regulatory Binder.

☐ Serious Adverse Events and IND Safety Reports

☐ Signature Log (Site Personnel Signature Sheet)

NOTE: This is a list of the signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

☐ Participant Identification List

NOTE: This is a confidential list of the names of all patients with their study identification number. It is maintained only at the site, and allows the investigator or institution to quickly identify study patients in the case of an emergency.

☐ Patient Screening Log/Registration Log

NOTE: This documents the chronological screening/enrollment of participants.

☐ Clinical Laboratory Certification (if required) and normal ranges

☐ Study Drug Documentation

- Drug Shipment and Receipt Records/Forms;
- Accountability Logs; and
- NCI Drug Accountability Record Forms (DARFs).

NOTE: Study drug documentation may be kept in the pharmacy, and not in the Regulatory Binder.

☐ Study Closeout Information

5.2 Source Documentation

Source documents are the original records of participant information (e.g., the medical record) and contain all the information related to a participant's protocol treatment. Source documents are used to verify the integrity of the study data, that the participant met the requirements for eligibility, and that procedures mandated in the protocol were followed. An investigator is required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record must originate in the patient's medical record.

5.2.1 List of Source Documents

Source documents may include but are not limited to the following items.

1. Institutional, research, clinic, or office records containing:
   - Inpatient and outpatient medical records;
   - Progress notes;
   - Consults;

- Nursing notes;
- Pathology reports;
- Radiology reports;
- Medicine/radiation administration records;
- Surgical Reports;
- Laboratory results;
- Admission forms;
- Flow sheets that are signed and dated;
- Protocol or study road maps;
- Appointment books; and
- Participant diaries/calendars.

2. Relevant participant-specific written communication from nonstudy health care providers, including comments related to past medical history, entry criteria, or other referral or followup information;

3. Clinical discharge summaries;

4. Participant-specific correspondence, such as documented telephone calls, email messages, and faxes; and

5. Obituaries, autopsy reports, and death certificates.

5.2.2 Source Documentation Guidelines

Source documents substantiate Case Report Form information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondences, etc.) must adhere to the following standards:

- Participant's name, date of birth, or medical record number included on each page;
- Legibly written in ink or clearly labeled;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant;

- Corrections made with a single line through the error, and then initialed and dated; and
- In addition, all laboratory reports, pathology reports, x-rays, and scans must have:
  - Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
  - Range of normal values for each result listed.

5.3 Case Report Forms

Participant information that relates to a clinical study is transferred from the source documents to Case Report Forms (CRFs). The PI or designee for each individual DCP study typically develop the CRFs for use in a particular study. However, DCP does provide sample CRF templates for use with Phase I and II DCP chemoprevention trials. These templates contain recommended content and formats and may be downloaded (http://www3.cancer.gov/prevention/pio/crf-forms.pdf or .wpd) and modified with study-specific information for each trial. Note section C 2 "Subject Enrollment Form" has a sub-section C2.3 "Race". The race criteria was updated January 2002. All studies approved after January 2002 should use the new criteria which can be found in the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, in section IV Definitions, letter E. Racial and Ethnic Categories. This policy can be found at the following website. http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

The Westat CRA will review participant CRFs to ensure that they are being filled out properly. The CRA will also verify that all data entered on the CRFs can be validated by information in the source documents. The CRA will also review the source documents to ensure that the pertinent information is included on the CRFs.

5.3.1 Completing a CRF

- Any assigned member of the study staff that has signed the Signature Form in the Clinical Trial Book may complete a CRF.

- CRFs should be completed within 1 week after the relevant information becomes available (i.e., the participant completes the visit or the laboratory results have been received).

- Enter information on the CRF with an ink (preferably black) pen only.

- The information documented on the CRF **must be identical** to the information found in the primary source document (i.e., participant charts, laboratory result printouts).

  NOTE: All source documents and CRFs must be available for verification by the Westat Team CRA during routine monitoring and auditing visits.

- If the information is **missing**, enter "ND" (no data) in the boxes/space. If the information is **unknown**, write "UNK" in the boxes/space. Entries of 'Missing' or 'Unknown' information must be explained in the source document (i.e., nurse's or clinic notes) for future verification.

- When boxes are provided for a response, please be sure to clearly mark the box to be selected with a ✓ or —. Make sure the mark is clear.

- Corrections are made in ink by crossing out the incorrect entry with a single horizontal line, placing the correct information next to the error, and providing an initial and date next to the correction. Do not backdate. Do not use any type of correction fluid or erase any entries on the forms.

- Do not write in the margins of the Case Report Forms. Any relevant additional information may be provided in the appropriate "comments" section.

- Avoid the use of abbreviations.

- CRFs are required for the following participants:

  - All participants who received a procedure required by protocol after signing informed consent;

  - All participants who have been randomized.

  NOTE: Not for participants screened and found to be ineligible.

5.4 Case Report Form (CRF) Notebook

Case Report Forms (CRFs) contain participant information related only to the study. Each participant has a Case Report Form Notebook (or another system to organize the participant's CRFs).

The CRF Notebook is arranged in a protocol-specific logical order. The forms in each section may be arranged chronologically or in reverse chronological order. In either case, there must be consistency throughout the notebook.

Each CRF should have complete participant identifying information and dated and signed entries. Each notebook should be organized into the following sections:

1. Demographic information
2. Pretreatment Section
    - Eligibility checklist
    - Registration/randomization forms
    - Confirmation of registration
    - On Study Form
    - Pathology Transmittal Forms
    - All other required forms to be completed and/or submitted prior to treatment
3. Treatment Section (arranged by cycle, study week, or other time point)
    - Treatment forms and/or flow sheet
    - Concomitant medications
    - Adverse Event and Serious Adverse Event Reports
    - Lab Data
4. Tumor evaluation/Response to treatment
    - Radiology Forms
    - Cytology Report
    - Pathology results
    - Bone Marrow aspiration results

5. Serious Adverse Events

   - Copy of supporting and followup documentation

6. Off Study

   - Off study forms

7. Followup Forms

   - Death Report form
   - Late adverse events documentation
   - Correspondence relating to patient status (relapse, additional treatment, etc.)

5.5 Record Retention

The Department of Health and Human Services and the Food and Drug Administration have regulations related to retention of protocol records.

- The Department Health and Human Services Regulations (45 CFR 46.115) applies for all research conducted or supported by any Federal department or agency. This regulation states that IRB records relating to research conducted shall be retained for at least 3 years after completion of the research. The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB Records must be retained for at least 3 years after completion of the research.

- Trials with a Food and Drug Administration (FDA) Investigational New Drug Application (IND) must additionally comply with 21 CFR 312.57 and 21 CFR 312.62. These regulations apply to investigational drug records, investigator financial interest records, and patient case histories. Both of these regulations require that the sponsor retain records and reports for 2 years after a marketing application is approved for the drug. If an application is not approved for the drug, the sponsor retains records and reports until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

6. SERIOUS ADVERSE EVENT REPORTING

6.1 Background

Serious Adverse Events (SAEs) are untoward clinical events experienced by a study participant while taking part in a clinical trial. Such events may be abnormal laboratory values, physical signs, or symptoms.

Specifically, an SAE is an event that results in one of the following outcomes:

- Death;
- Life-threatening event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- A congenital anomaly/birth defect; or
- An important medical event that may not result in death, be life threatening or require hospitalization though, based upon appropriate medical judgement, may jeopardize the participant and may require medical or surgical intervention to prevent one of the previously identified outcomes.

Grade 3 events (per NCI Common Toxicity Criteria Version 2.0) which can be accessed at website http://ctep.cancer.gov/reporting/ctc.html that fit the above criteria will be treated as SAEs. **All** Grade 4 events will be considered SAEs and will be handled as described below.

Clinical investigators are required to report SAEs to the sponsors and their local IRB. The protocol sponsor, NCI/DCP, is required to review and report SAEs, as *safety reports*, to the FDA. The FDA compiles this information for the purpose of (1) identifying early warnings; (2) determining safety of the drug during the New Drug Application (NDA) process; and (3) including information in the package insert of approved drugs.

DCP has contracted with CCS Associates to manage all regulatory and serious adverse event issues related to DCP clinical trials. CCS Associates will receive and process SAE reports from the sites and will serve as a liaison between clinical sites, DCP, and the FDA.

6.2 Reporting Process

All SAEs must be reported in an expedited manner (see Figure 6-1):

- In the interest of participant safety in DCP studies and to fulfill regulatory requirements, all SAEs, whether related to the study agent or not, will be reported to the sponsor (NCI/DCP) by telephone or fax within 24 hours, and in writing within 48 hours, of the Principal Investigator learning of the event. The written information shall be documented on the "NCI Division of Cancer Prevention Serious Adverse Event Form." See Appendix C and/or http://www3.cancer.gov/prevention/pio/instructions.html for a copy of this reporting form.

- The PI or designee, CCS Associates, also receives the written report within 48 hours. CCS Associates works with the study site staff and DCP staff to ensure that all required information is obtained.

- All SAEs must be entered in the Adverse Event Case Report Form as part of the cumulative participant report and must also be reported in the Investigator Progress Reports that are submitted to DCP at specified intervals. (See Appendix D for a sample of the form.)

- The PI must report all SAEs to the local IRB.

SAE Reporting Process

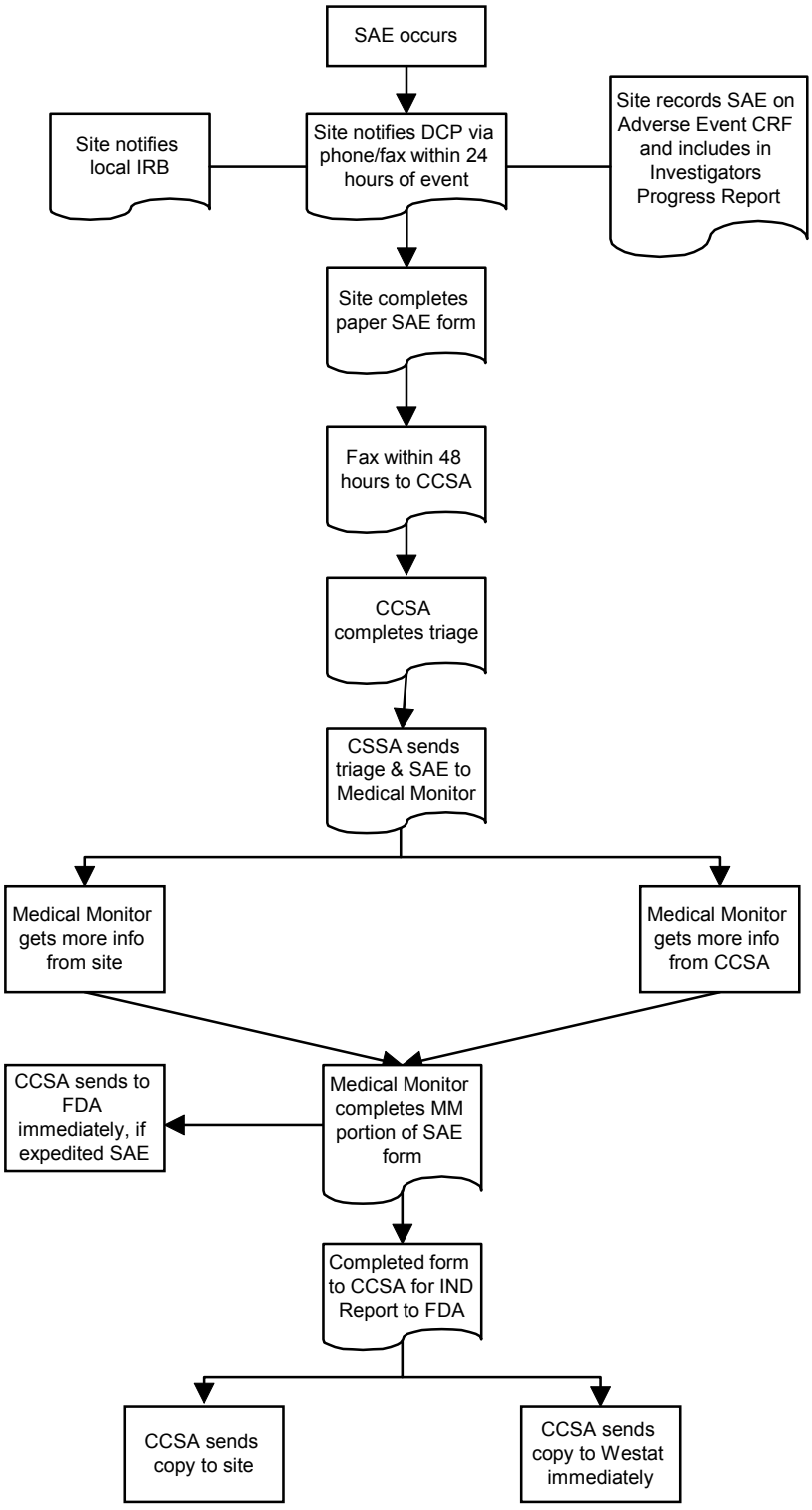

Figure 6-1. SAE reporting process

The contact information for telephone calls and written reports is as follows:

Phone calls or fax within 24 hours of SAE to DCP:

Medical Monitor (as specified in the contract)
DCP/National Cancer Institute/NIH
Refer to Appendix A for complete contact information.

** When calling or faxing, please include date, time, your name, phone number, affiliation, reason for calling/faxing, NCI contract and protocol number.

The contact information for he Medical Monitor or CCS will vary depending upon the protocol.

6.3 Serious Adverse Event (SAE) Report Form Submission

Submission of DCP SAE form within 48 hours of SAE to:

1. Medical Monitor (as specified in the contract/protocol)
   DCP/National Cancer Institute/NIH
   Executive Plaza North, Suite 201
   9000 Rockville Pike
   Bethesda, MD 20892-7340
   Fax: 301-435-3541

   Alternate address for Express Mail or hand delivery:

   Executive Plaza North, Suite 201
   6130 Executive Blvd.
   Rockville, MD 20852

2. Kathleen Dolan, RN,MS
   CCS Associates, Inc.
   2005 Landing Drive
   Mountain View, CA 94043
   Kdolan@ccsainc.com
   Fax: 650-691-4410

6.4 SAEs and Site Monitoring

- The Westat CRA receives SAE reports from CCS Associates and will review them prior to a study site visit.

- During a site visit, the CRA will ensure that site staff has:
  - Appropriately filed the SAE documentation with CCS Associates;
  - Recorded the serious adverse event on the appropriate CRF; and
  - Notified the local IRB.
- If the CRA identifies any unreported SAEs during a monitoring visit, the site staff will report and document the information with guidance from the CRA.
- SAE assessment is included in the Site Monitoring Visit Report completed by the CRA that is submitted to DCP and the clinical site.

7. PROTOCOL DEVIATION REPORTING

7.1 Background

DCP, as a protocol sponsor, is responsible for implementing and maintaining quality assurance/quality control Standard Operating Procedures (SOPs) to ensure that studies are conducted according to the protocol (compliance), Good Clinical Practice (GCP) and all applicable regulatory and DCP requirements. A protocol deviation is any noncompliance with the protocol, Good Clinical Practice, regulatory standards, or DCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. The term "deviation" is not to be confused with the term "deficiency." The term deficiency is used by the CRA to assess site performance at a monitoring visit.

It is the responsibility of the site staff to identify deviations as they occur and to report deviations to the DCP Medical Monitor. Corrective actions are developed by the site and implemented promptly. These practices are consistent with Good Clinical Practice §4.5.1, §4.5.2, §4.5.3, §5.1.1, §5.20.1, and §5.20.2.

The relationship of deviation reporting to monitoring visits is that frequently the clinical research associate (CRA) identifies deviations during a study site-monitoring visit. If this occurs, the CRA will instruct the study site staff to report the deviation to the Medical Monitor and local IRBs. While deviations may be discovered during a site visit, sites should not rely on the monitoring visit alone to identify and report deviations. It remains the responsibility of the site to use continuous vigilance in the detection and reporting of deviations to DCP as soon as they occur.

7.2 Purpose

The identification and reporting of deviations critically impacts both the conduct and analysis of a clinical trial. For example, a consistent pattern of a particular deviation may reveal the need to amend the protocol to improve subject compliance. Numerous deviations related to the collection of safety data may impact the analysis of study data. Recognizing trends and patterns of deviations allow the Principal Investigator to correct operational issues and to perform continuous quality improvement.

Standardizing the process of detecting and reporting deviations will promote the following outcomes:

- Early identification of deviation trends that require corrective action by the study site staff.
- Rapid correction of protocol problems (when appropriate) in response to deviation trends.
- Prompt (i.e., real time) reporting by site staff of protocol deviations.
- More accurate statistical analysis of the protocol outcomes with integration of deviations data.
- Consistent followup of corrective action to evaluate effectiveness.
- Consistent expectations for monitoring DCP-sponsored protocols for compliance.
- Identification of study site staff educational needs.
- Performance data for annual site contract evaluation.

7.3 Procedure

The expected outcome would be that the study site staff is knowledgeable about the protocol, and follows the protocol as outlined. If the study staff has questions about the protocol, the Principal Investigator, DCP Medical Monitor, or nurse specialist should be consulted. (Check Appendix A for the telephone numbers and email addresses of the DCP staff.)

- When a protocol deviation is identified, the PI, or designee:
  - Documents the deviation and specifies the sections of the protocol related to the deviation, using the Protocol Deviation Notification Form in Appendix D.
  - Describes corrective action taken to minimize the risk of a repeat occurrence of the deviation.
  - Signs the completed Protocol Deviation Notification Form.
  - Faxes the completed Protocol Deviation Notification Form to the DCP Medical Monitor. See Appendix A, Accessing the DCP and Westat Team.

- Upon receipt of the Protocol Deviation Notification Form, the medical monitor or designee will:
  - Confirm the deviation is a bona fide protocol deviation.
  - Review the corrective action plan and determine if the plan is acceptable or requires additional action plans. If additional action plans are required, work with the PI or designee to ensure that appropriate corrective action plans are developed and implemented.
  - Sign the Protocol Deviation Notification Form.
  - Fax the Protocol Deviation Notification Form to Westat. See Appendix A, Accessing the DCP and Westat Team.
  - Follow up with site staff to ensure that the corrective action plan is implemented and no other deviations of that type have occurred.
- Upon receipt of the Protocol Deviation Notification Form, the Westat project director will:
  - Distribute a copy of the completed Protocol Deviation Notification Form to the study site.
  - Review the deviation and corrective action with the audit manager and the CRA for the site. There may be collaboration with the site staff, DCP Medical Monitor, and Westat staff to resolve outstanding issues related to the action plans and/or implementation of the action plans.
  - Log the deviation information into the Deviation Database.
  - Distribute the Protocol Deviation Notification Form to CCS Associates.
  - Create standardized reports according to needs identified by DCP, such as deviation type, frequency, severity, etc.

7.4 Examples of Deviations

Deviations, or noncompliance, may result from the action of the subject, investigator, or study site staff. Frequently noncompliance is not attributable to an error and should not be viewed as punitive in nature; it is simply an occurrence that deviates, or does not comply with the protocol. In other situations, the deviation may have a more serious impact on the conduct or the outcome of the trial. Repeated deviations of a similar type are particularly important as they may signal the need for change

(i.e., protocol, operations, communication). Deviations are viewed as an opportunity to make improvements and may signal the need for education.

The following are provided as samples of noncompliance with the protocol, GCP, or DCP guidelines that should be reported as deviations:

- Missed study assessments according to the required protocol guidelines;
- Errors in dispensing the study agent in the right dose, or administering at the right time or to the right patient, or incorrect agent administered;
- Informed consent not obtained prior to enrollment or failure to use the correct version of the informed consent;
- Consent form is missing, or consent form was not signed and dated by patient;
- Consent form does not include updates of information distributed as an amendment to the protocol;
- Missing Case Report Forms or repeated missing data on Case Report Forms;
- Adverse Event or Serious Adverse Event not reported according to DCP guidelines;
- Participant enrolled in a study who did not meet the eligibility criteria as specified in the protocol;
- Source documents are missing or are missing documentation to support information reported on the CRF;
- Additional agent/treatment used which is not permitted by protocol;
- Unjustified dose modifications or failure to modify doses according to protocol;
- Unjustified (and/or undocumented) delays in treatment; and
- Protocol never approved by IRB, or other IRB violations.

8. CHANGE IN PARTICIPANT STATUS

8.1 Off Study Agent

If a participant is permanently discontinued from the study agent, the participant status becomes Off Study Agent, and the participant continues to be followed for survival and disease progression as specified by the protocol. (The medical monitor must first be consulted regarding decisions to permanently discontinue the study agent.) Participants may have the study agent permanently discontinued for a number of reasons including:

- AE/SAE such as severe allergic reaction (examples are exfoliative erythroderma, anaphylaxis, or vascular collapse);
- Unresolved toxicities and/or disease progression (see protocol for specific criteria);
- Investigator initiated, DCP, FDA, or pharmaceutical sponsor discontinuations
  - Inadequate supply (i.e., participant has no agent or site has no agent);
  - Participant noncompliance (protocol-specific);
  - Concomitant exclusionary agent (protocol specific, e.g., NSAIDS);
  - Medical contraindication (pregnancy);
- Patient initiated discontinuation
  - Withdrew consent;
  - Refused treatment;
  - Other;
- Completion of the protocol; and
- Other.

When a participant is permanently discontinued from the study agent treatment, the final study visit, clinical, and laboratory evaluations must be obtained. All study agents or treatment materials need to be returned.

8.1.1 Required Followup for Off Study Agent Status

The study forms required at the time of permanent discontinuation of a study agent are specified in the Off Study Agent section in the protocol. Once the "Off Study Agent" clinical evaluations are completed, the participant may be followed for disease progression and survival. The frequency of followup evaluations is specified by the protocol.

8.1.2 Off Study

Participants who are considered to be "off study" are those who are permanently discontinued from study agent and do not wish to participate in the study any longer. They do not require followup. The following are some reasons a participant can go off study:

- Completion of the protocol(treatment, assessments, and protocol-dictated followup);
- AE/SAE;
- Death (complete Death Report form);
- Lost to followup;
- Investigator initiated discontinuation
  - Inadequate agent supply;
  - Non-compliant patient;
  - Concomitant medication;
  - Medical contraindications (e.g. disease progression, pregnancy);
  - Others;
- Patient initiated discontinuation
  - Withdrew consent;
  - Refused treatment, assessments;
  - Other (please specify);

- Inability to contact participant after repeated attempts; and
- Other.

8.2 Death

All deaths of participants at DCP-funded clinical sites need to be reported as a Serious Adverse Event (SAE) regardless of the relationship to the study agent or time off study. The SAE report is forwarded to the DCP Medical Monitor for review. For information about timeframes for submission of SAE forms and further instructions, please refer to the SAE procedures in Chapter 6 of this manual.

The SAE form should be completed and faxed to the DCP Medical Monitor. Deaths also need to be reported using the protocol-specific death form. One Death Report form needs to be completed for each protocol in which the participant was enrolled. The following information should be submitted on the SAE form at the time the event is reported:

- Name and phone number of the reporter;
- Participant's PID number;
- Date of death;
- Primary cause of death;
- Name of study treatment(s);
- Date treatment(s) last given;
- Is death related to study treatment; and
- Brief history leading to death. (Submit autopsy report if available.)

9. SITE MONITORING VISITS BY WESTAT TEAM

9.1 Three Types of Site Visits

Westat Clinical Research Associates (CRAs) conduct three types of site visits: initiation, annual/interim, and close-out visits. Each of these will be discussed separately below. The DCP Medical Monitor and the Organ Research Group nurse specialist may choose to participate in each of these visits.

9.1.1 Initiation Visit

Purpose

The purpose of the initiation visit is to:

- Meet with key staff (Principal Investigator, study coordinator, pharmacist, lab technician, etc.) at the site who will participate in the conduct of the clinical trials which will be monitored by the Westat Team. If there are multiple sites involved in a study, it is expected that key staff including the co-investigators, study coordinators, and research nurses from each of the participating sites will be present at the lead site for the visit.
- Orient staff to all general aspects of the performance of the work.
- Discuss the roles and responsibilities of DCP, clinical site staff, and Westat Team staff.

Scheduling

The initiation visit will usually be accomplished in one day and occurs when the site is ready to begin the study but no participants have been enrolled. The Westat site monitoring task manager will discuss plans to conduct the visit with the DCP Medical Monitor and the Principal Investigator. The monitoring task manager (or designee) will send a letter confirming the visit and an agenda in advance of the initiation visit. The DCP Medical Monitor approves both the letter and the agenda.

Conduct of Visit

An initiation visit is a meeting with all study site staff who will be involved in the conduct of the clinical research. Topics discussed at an initiation visit will include, but are not limited to, the following:

- Role of DCP staff;
- Background and purpose of study;
- Study procedures;
- Protocol initiation and enrollment;
- Participant recruitment and retention strategies;
- Adverse event reporting;
- Toxicity management;
- Endpoint and treatment discontinuation;
- Data collection and data management;
- Source documentation/confidentiality;
- Policy and procedures manuals;
- Regulatory documentation and CCS Associate's role;
- Recordkeeping requirements;
- Laboratory procedures;
- Unblinding procedures;
- Pharmacy;
- Quality Assurance (QA) procedures;
- Communication;
- Site management;
- Handling protocol deviations; and
- Site monitoring.

Assignment of each agenda item is planned in advance. An initiation visit may include a tour of the physical facility.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will draft a summary report of the visit, which is reviewed by the Medical Monitor. A copy of the report format is in Appendix F. Site personnel will receive a copy of the site monitor's initiation visit report 4-6 weeks after the visit, once the report has been finalized as approved by the DCP Medical Monitor.

9.1.2 Annual/Interim Visit

Purpose

Westat CRAs conduct annual site visits at least once a year at all "lead organizations", unless the requirement is waived by the DCP Project Officer. An interim visit can be scheduled at any time if the protocol is rapidly accruing or if deficiencies are discovered. The purpose of the annual/interim site visit is to determine that:

- Facilities used by the investigator are acceptable for the study's purposes;
- There is compliance to the study protocol or investigational plan;
- Changes to the protocol and/or consent have been approved by the IRB and/or reported to the client and the IRB;
- Protocol deviations are recorded and reported appropriately;
- Participants have signed informed consents prior to the conduct of study visits;
- There is accurate reporting of significant events; clinical endpoints, adverse events (AEs) and serious adverse events (SAEs);
- Accurate, complete, and timely reports are being made to DCP, CCS Associates, and the IRB; and
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

Scheduling

An annual/interim monitoring visit is accomplished in 2 or 3 days. The Westat site monitoring task manager will discuss plans to conduct the visit with the DCP Medical Monitor and the Principal Investigator at least 6 weeks in advance of the visit. The monitoring task manager will send a letter confirming the visit to the Principal Investigator and site study coordinator stating the purpose and objectives of the visit, the staff and documents to be available, and the expected duration of the visit. At least 2 weeks prior to the visit, the site monitor will notify the site study coordinator of charts to be reviewed. At least two additional charts (not previously requested) from the lead institution will be reviewed at each annual visit.

Requirements

The following must be available for the CRA upon arrival for a site visit:

- Site monitoring sign-in log;
- PID logbook;
- Case Report Forms notebooks;
- Binders containing copies of signed informed consents for all study participants;
- Source documentation, including clinic charts, shadow files, and hospital charts if relevant;
- Regulatory documents;
- Appointment to meet with the site pharmacist, if a pharmacy audit is being performed; and
- A quiet well-lit area for the monitor's use each day during the site visit.

In addition, the coordinator or designated staff should be available each day to review findings and provide additional records that may be requested by the monitor. Finally, time should be set aside at the conclusion of the visit for the study coordinator and Principal Investigator to meet with the site monitor to discuss the monitoring findings, site performance parameters, and any outstanding issues.

Conduct of Visit

The site monitor will perform the following during the annual visit:

- Confirm the following regulatory documents are on file:
  - IRB approval letters;
  - IRB letters of annual approval;
  - IRB-approved consents;
  - Form FDA 1572s;
  - Laboratory certificates;
  - Laboratory normal values;
  - Screening logs;
  - Safety reports and memos with appropriate IRB correspondence; and
  - Other IRB correspondence.
- Ensure sensitive documents are stored appropriately
- Perform CRF and record review. The following data will be verified against source documents:
  - Signed and dated informed consent, obtained prior to the pre-entry workup;
  - Inclusion/exclusion criteria;
  - Visit dates;
  - Clinical and laboratory evaluations;
  - Concomitant medications;
  - Adverse events;
  - Concurrent illness; and
  - Adherence to protocol.

The number of records that will be reviewed is dependent upon the number of patients enrolled in the study. Records will be selected from the lead site and participating sites when applicable.

NOTE: Participating sites will be instructed as to the process of procuring participant records to the lead site for the CRA's review.

The site monitor will verify eligibility and perform chart reviews for a minimum of 7 or 25 percent (whichever is greater) of participant records per study. Except for the two unannounced records, the study coordinator will be notified in advance of which records will be reviewed. Informed consents will be reviewed for 100 percent of enrolled participants. The Westat Team CRA will also:

- Conduct pharmacy audit
  - Review of pharmacy-related regulatory documentation;
  - Examine procedures for:
    1. Investigational agent storage
    2. Investigational agent distribution
    3. Investigational agent security
  - Compare shelf inventory (bottle count) versus the Drug Accountability Record Form (DARF);
  - Audit participant records to compare investigational agent dispensed as recorded on the DARF versus that recorded as administered in the source document;
  - Compare the DARF with the protocol registration listing along with dose to ensure that participants who received investigational agents were registered on the specified protocol;
  - Verify accuracy of investigational agent preparation and calculation of dosage; and
  - Authenticate that any unopened/unused or expired investigational agent containers are returned to DCP.
- Assess site operations
  - Verify adequate resources (e.g., facilities, staffing);
  - Review internal QA activities;
  - Review adequacy of number of subjects available/recruited for the study;

- Review adequacy of priority given to the study;
- Followup on problems previously identified;

- Conduct a summary meeting with the Principal Investigator, pharmacist, and study staff to review the findings of the site visit. During this meeting the findings identified during the course of the site monitoring visit will be discussed, and recommendations for improvement will be made.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will draft a summary report of the visit, which is reviewed by the Medical Monitor. A copy of the report format is in Appendix G. Site personnel will receive a copy of the site monitor's annual visit report 4-6 weeks after the visit, once the report has been finalized as approved by the DCP Medical Monitor.

9.1.3 Close-out Visit

Purpose

A Westat CRA will typically conduct a close-out visit to a study site within 60 days of study termination. This is often done after the "draft final report" has been submitted to DCP, but before the final version of the report is submitted. The purpose of this visit is to:

- Formally bring closure to the study at the site;
- Ensure all data have been collected;
- Complete the final accounting and disposition of the study agent; and
- Verify that the investigator's files are complete.

The close-out visit for a particular protocol may be combined with elements of an annual site visit in specific situations.

Scheduling

A close-out visit will generally take one day, but may require more. The Westat site monitoring task manager will discuss plans to conduct the visit with the DCP Medical Monitor and the Principal Investigator at least 6 weeks in advance of the visit. The site monitoring task manager will send a letter confirming the visit to the Principal Investigator and site study coordinator stating the purpose and objectives of the visit, the staff and documents to be available, and the expected duration of the visit.

Requirements

The requirements for a close-out visit are the same as for an annual/interim visit (see page 9-4).

Conduct of Visit

During the close-out visit, the Westat site monitor will perform the following:

- Ensure that all case report forms for each subject have been completed.
  - Verify that all data have been keyed on-site or all forms have been submitted to the coordinating center or the protocol-specified destination.
  - If the data forms have not been completed, keyed, or submitted, the monitor will discuss with the investigator and study coordinator a timeline for accomplishing these tasks.
- Verify that a signed informed consent is on file for each study participant.
- Review the status of all outstanding data edits, queries, or delinquent forms and timeline for their resolution.
- Confirm that the IRB/IEC has been informed of the study closure.
- Verify that all regulatory and other pertinent documents for the protocol (IRB approvals, consent documents, etc.) are up to date and on file.
- Verify that the investigator knows to submit a final report to DCP, and that a deadline for completion has been identified.

- Ensure that a progress note is included in each participant's medical record indicating that study participation has ended.

- Ensure that the Principal Investigator understands the requirements for reporting of adverse events for subjects who have completed the study.

- Ensure that the Principal Investigator understands the requirements for retention of study records. (The investigator must keep study records for 2 years after approval of a marketing application. If not approved, the records must be kept for 2 years after the FDA has been notified of the discontinuation of an IND by the sponsor).

- If applicable, determine the disposition of participant specimens obtained during the study and stored on site. Ensure all specimens have been sent to the appropriate place/facility or that the Principal Investigator understands the plan for future shipment.

- Meet with the site pharmacist to determine the disposition of remaining study agent and ensure that it has been returned to the repository. Ensure all required drug accountability has been reconciled and forms have been completed appropriately. If a blinded study drug was used, confirm that the tear-off labels were not opened. For any that were opened, documentation should be obtained noting the reason for unblinding.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will draft a summary report of the visit, which is reviewed by the Medical Monitor. A copy of the report format is in Appendix H. Site personnel will receive a copy of the site monitor's initiation visit report 4-6 weeks after the visit, once the report has been finalized as approved by the DCP Medical Monitor.

Appendix A

Accessing the Division of Cancer Prevention, Westat, and CCSA

APPENDIX A.
ACCESSING THE DIVISION OF CANCER PREVENTION, WESTAT AND CCSA

DCP Address:	Division of Cancer Prevention National Cancer Institute 6130 Executive Boulevard Bethesda, Maryland 20892 T: 301-496-0090 F: 301-435-3541
Westat Address:	Westat 1441 West Montgomery Avenue Rockville, Maryland 20850-2062 T: 301-294-2885 F: 301-738-8379
CCS Associates Address:	CCS Associates, Inc. 2005 Landing Drive Mountain View, CA 94043 T: 650-691-4400 F: 650-691-4410
Help Line at Westat:	1-888-662-8354 Business hours are between 8:00 am and 4:30 p.m. (ET) Monday through Friday. The caller is asked to leave a detailed voice message outlining the information needed. Westat staff checks the Help Line every two hours during business hours. Calls will be triaged to the appropriate individual for followup. The caller will receive a response as soon as possible. If there is an immediate need, contact the respective Organ System Group nurse specialist.
Protocol Information Office: For protocol development, review, amendment approval	**Head and Project Officer:** Linda Parreco, RN, MS T: 301-496-0090 F: 301-435-3541 E: parrecol@mail.nih.gov

Organ System Groups:

Breast and GYN	**Chief:**	Karen Johnson, MD, Ph.D., MPH T: 301-402-3666 F: 301-480-9939 E: johnsonn@mail.nih.gov
	Nurse Specialist:	Kathleen Foster, RN T: 301-402-6211 F: 301-480-9939 E: fosterk@mail.nih.gov
Chemoprevention Agent Development Research Group	**Chief:**	James Crowell, Ph.D. T: 301-594-0459 F: 301-70-0553 E: jcrowell@mail.nih.gov
		Marjorie Perloff, MD T: 301-594-0466 F: 301-402-0553 E: perloffm@mail.nih.gov
		Martha Basinger T: 301-594-0422 F: 301-402-0553 E: basingem@mail.nih.gov
GI and other	**Chief:**	Ernest Hawk, MD, MPH T: 301-594-2684 F: 301-435-6344 E: hawke@mail.nih.gov
	Nurse Specialist:	Ellen Richmond, RN, MS T: 301-435-2466 F: 301-435-4644 E: richmone@mail.nih.gov
Lung and Upper Aerodigestive	**Chief:**	Eva Szabo, MD T: 301-435-2456 F: 301-480-3924 E: szaboe@mail.nih.gov
	Nurse Specialist:	Judy Smith, RN, MSN T: 301-496-7469 F: 301-480-3924 E: jjsmith@box-j.nih.gov

Prostate and Urologic	**Chief:**	Howard Parnes, MD T: 301-402-3606 F: 301-435-1564 E: parnesh@mail.nih.gov
	Nurse Specialist:	Maggie House, BSN T: 301-594-1579 F: 301-433-1564 E: housem@mail.nih.gov

Regulatory:

OHRP, IRB	Margaret Scheitrum T: 650-691-4400 x 127 F: 650-691-4410 E: mscheitrum@ccsainc.com
IND	Linda Doody, Ph.D T: 650-691-4400 x 107 F: 650-691-4410 E: ldoody@ccsainc.com
SAE	Kathleen Dolan, RN, MS T: 650-691-4400 x 115 F: 650-691-4410 E: kdolan@ccsainc.com

Westat Project Staff:

Project Director	Nancy Dianis, RN, MS T: 301-294-2885 F: 301-738-8379 E: nancydianis@westat.com
Data Monitoring	Denise Pearson T: 301-517-8038 F: 301-738-8379 E: denisepearson@westat.com
Study Site Auditing	Detra Robinson, MA T: 301-738-3653 F: 301-738-8379 E: detrarobinson@westat.com
Site Staff Education and Training	Erin Iturriaga, RN, CRCC T: 301-738-3675 F: 301-738-8379 E: eriniturriaga@westat.com

Maintain Centralized Database and Informatics		Lisa Chatterjee T: 301-451-6368 F: 301-384-8877 E: lisa.chatterjerr@oracle.com
NCI Staff:	**Acting Deputy Director; Associate Director for Clinical Research; Project Director:**	Leslie Ford, MD T: 301-496-0265 F: 301-435-3541 E: fordl@mail.nih.gov
	Project Officer:	Jennifer Flach T: 301-496-0265 F: 301-435-0031 E: flachj@mail.nih.gov
	Project Officer:	Rose Mary Padberg, RN, MS T: 301-4996-0265 F: 301-435-3541 E: padberg@mail.nih.gov
	Program Director:	Izet Kapentanovic, Ph.D. T: 301-435-5011 F: 301-402-0553 E: kapentani@mail.nih.gov
	Contract Officers:	Gary Topper T: 301-435-3793 F: 301-402-8579 E: topperg@amb.nci.nih.gov Theresa Shroff T: 301-435-3796 F: 301-402-8579 E: shrofft@amb.nci.nih.gov Schyuler Eldridge T: 301-435-3794 F: 301-402-8579 E: eldridgs@rcb.nci.nih.gov

	Administrative Program Assistant:	Myra Terrell T: 301-402-3668 F: 301-435-1894 E: terrellm@mail.nih.gov
Theradex Staff: Westat Team Subcontractor		Hank Durivage, Pharm D T: 609-799-7580 ext. 347 F: 609-799-1567 E Hdurivage@theradex.com
		Kelly O'Hern, RN T: 609-799-7850 ext. 373 F: 609-799-4148 E: Kohern@theradex.com
		Rolee Pathak, Pharm D T: 609-799-7850 ext. 367 F: 609-799-4148 E: Rpathak@theradex.com

Appendix B

Glossary of Terms

APPENDIX B. GLOSSARY OF TERMS

DIVISION OF CANCER PREVENTION GLOSSARY OF TERMS

Acronym	Term	Definition
AE	Adverse Event	Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution is unrelated, unlikely, possible, probable, or definite).
	Agent	A pharmaceutical drug used individually or a combination of them that is being tested in a cancer prevention trial.
	Auditing	The act of reviewing and evaluating particular components at a site visit: (1) conformance to IRB and consent form requirements, (2) pharmacy and drug accountability, and (3) patient case review.
	Audit Task Manager	An appropriately qualified Westat employee, by training and experience, whose responsibilities include, but are not limited to, DCP project goal planning for on-site monitoring, supervision of staff, assignment of protocol(s) and sites to monitor, assuring compliance with specific SOPs, and assuring that on-site monitoring visits are conducted, and that site visit reports are recorded appropriately.
	Amendment	A change to an approved clinical protocol which significantly affects the safety of the subjects, the scope of the investigation, or the scientific quality of the study. May also include administrative or minor changes, such as changes in company personnel, spelling error, etc.
	Biomarker	A substance sometimes found in an increased amount in the blood, other bodily fluids, or tissues and which may mean a certain type of cancer is in the body. Examples of biomarkers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, gastrointestinal tract cancers), and PSA (prostate cancers).
BGCRG		Breast and Gynecological Cancer Research Group, an organ system group within DCP.

Acronym	Term	Definition
CADRG		Chemopreventive Agent Development Research Group, an organ system group within DCP.
CB		Chemoprevention Branch
CFR	Code of Federal Regulations	The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the Executive Departments and the agencies of the Federal Government.
CRF	Case Report Form	A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each clinical trial.
CCSA	CCS Associate	A DCP contractor who is responsible for assisting the PIO, Organ Site Research Group personnel and study staff with protocol development and management of regulatory issues.
	CLIENT	A desktop machine in which users can interact and run applications.
	Clinical Investigation	Any experiment in which a drug is administered or dispensed to, or used, involving one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.
CRA	Clinical Research Associate (the monitor)	An appropriately qualified employee, by training and experience, who is responsible for assuring that clinical trials are conducted according to appropriate procedures and all applicable government regulations. The CRA is also responsible for conducting on-site visits to clinical centers to verify subject eligibility, data accuracy, and compliance with regulatory requirements.
	Commercial Agent	Any agent not supplied under an IND but obtained instead from a commercial source.
CDE	Common Data Element	A standardized vocabulary with technical specifications, used to define data elements in NCI.
CTC	Common Toxicity Criteria	A descriptive terminology, which is to be utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Acronym	Term	Definition
	Confidential Information	Any data that should not be in the public domain. This includes information that may be associated with an individual patient, the personal identification of individual patients, information about participating investigators and institutions that are not already part of the public record; information regarded as proprietary by participants in DCP supported research protocols.
CRO	Contract Research Organization	A commercial organization that assumes, as an independent contractor with a sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, site monitoring visits, statistical analysis, and preparation of reports to be submitted to the Food and Drug Administration.
	Control Group	In phase III cancer prevention clinical trial of a study agent, the group that receives either a placebo or a standard agent that is being compared to a new agent.
CSAERS		Chemoprevention Serious Adverse Event Reporting System
CV	Curriculum Vitae	Document that outlines a person's educational and professional work history.
DARF		Drug Accountability Report Form
DCP		Division of Cancer Prevention
DESK	DCP Enterprise System Knowledgebase	The computer system knowledgebase that supports DCP data such as agents and address modules.
	Dropout	A participant who does not complete a clinical trial. Subjects may discontinue participation due to disease-related, medication-related, clinical trial-related reasons, or due to the participant's own volition.
	Drug Accountability	Maintaining current and accurate records showing the quantities of drug received, dispensed, stored at the site, and returned to the sponsor.

Acronym	Term	Definition
	Database Administrator	A systems professional trained in database administration techniques and responsible for utilizing these techniques to manage security and performance of an Oracle database. These responsibilities include: creating and removing user accounts, developing appropriate access roles and profiles, controlling and monitoring user access, identification of security violations, backup and recovery of the database, and monitoring and optimizing performance. There will be a primary and secondary project database administrator for Oracle Clinical database on the DCP project. A corporate database administrator is responsible for establishing policies and procedures for all Oracle databases at Westat.
DSMB	Data and Safety Monitoring Board	An impartial group of researchers who periodically review data from blinded, placebo-controlled trials. A DSMB can stop a trial if toxicities are found or if treatment is proven beneficial.
	Effectiveness	The desired measure of a drug's influence on a disease condition as proven by substantial evidence from adequate and well controlled investigations. Reasonable assurance that in a significant portion of the target population, the use of the drug will provide clinically significant results; that the drug has a beneficial therapeutic effect (how well does the treatment work from the individual patient's perspective and the impact of health care resource utilization overall).
	Efficacy	A product's ability to produce beneficial effects. (Does it do what we intended it to do, or what we are claiming it can do?)
EC	Ethics Committee	An independent body comprised of medical professionals and non-medical members whose responsibility is to verify the integrity of the research, and human rights of the subjects participating in a particular trial are protected, thereby providing public reassurance. See Institutional Review Boards (IRBs).
	Evaluable Subject	A subject who meets the criteria for evaluation described in the protocol or the statistical plan. Subjects with protocol violations are not evaluable.
FDA	Food and Drug Administration	An agency of the U.S. Government which oversees the study of investigational drugs and grants marketing approval for new drugs. Regulates the drug development and clinical trials industry.

Acronym	Term	Definition
	Form FDA 1572	Statement of the investigator that outlines the responsibilities that the investigator agrees to assume in order to conduct the clinical trial.
	Global Librarian	A person assigned the responsibility of internal administration and change management of the Global Library in an Oracle Clinical database. This person is also assigned the responsibility of granting and revoking access for individual users to specific protocols.
GOCRG		Gastrointestinal and Other Cancer Research Group, an organ system group in DCP.
GCP	Good Clinical Practice	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
HIPAA		Health Insurance Portability and Accountability Act
	Human Subject	An individual participating in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.
HTML	Hyper Text Markup Language	A document-layout and hyperlink-specific language. It tells the browser how to display the content of the document.
HTTP	Hyper Text Transfer Protocol	A standard through which a client browser talks to a server to load the requested document.
IB	Investigator's Brochure	A collection of data known to date about the investigational drug, both clinical and preclinical data (Also referred to as Clinical Investigation Brochure or Investigational Drug Brochure).
	Informatics	Information science.
IC	Informed Consent	A process in which a person learns key facts about a clinical trial, including potential risks and benefits, before deciding whether or not to participate in a study. Informed consent continues throughout the trial.
ICF	Informed Consent Form	The legal written record where the subject, or his/her representative, agrees to voluntarily participate in the investigation.

Acronym	Term	Definition
	Initiation Visit	A type of site visit conducted to verify that all regulatory and other requirements are in place prior to implementing a study.
IRB	Institutional Review Board	A committee constituted according to requirements established by the NIH Office for Human Research Protections and having the responsibility for reviewing, approving, and monitoring the conduct of clinical research protocols for their institutions.
ICH	International Conference on Harmonisation	A committee of US, EU, and Japanese members organized to develop guidelines for the conduct of clinical trials (this applies to pharmaceutical products).
IND	Investigational New Drug Application	The application filed with the FDA informing them of the sponsor's intent to begin testing a new pharmaceutical product in humans.
	Investigational Agent	An agent sponsored under an Investigational New Drug Application (IND).
	Investigator	An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the agent is administered or dispensed to a subject). In the event a team of individuals conducts an investigation, the investigator is the responsible leader of the team.
	JavaScript	Lightweight Java-based scripting language used at client web browsers to perform basic web page validation and processes.
KA	Knowledge Acquisition	The formalized process of collecting information about business organizational processes necessary for developing requirements.
	Lead Organization	The institution holding the funding agreement with the NCI, which is the institution of the Principal Investigator.
LUACG		Lung and Upper Aerodigestive Cancer Group, an organ system group within DCP.
	Marketing Application	An application for a new drug submitted under section 505(b) of the act of biologics license application for a biological product submitted under the Public Health Service Act.

Acronym	Term	Definition
	Medical Site Monitor	A medically trained DCP employee, whose responsibilities include, but are not limited to, interacting with the investigator(s) and staff at the clinical site on all clinical matters related to the study and to oversee the study from a safety standpoint.
	Monitoring	The act of overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPS), GCPs, and the applicable regulatory requirements.
NCICB		National Cancer Center for Bioinformatics
	Oracle Clinical	A software product of the Oracle Corporation designed to meet the needs of the clinical trials industry.
	Organ System Group	A specific network of physicians, nurse specialists, and other health professionals at DCP who monitor and evaluate the scientific integrity of organ-specific diseases in contracts, grants, and other long-term projects.
	Participating Organization	Institutions who by arrangement with the NCI/DCP and the lead organization participate in a clinical trial by accruing patients.
PIMS		Protocol Information Management System
	Placebo	A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug.
	Project Director	An appropriately qualified Westat employee, by training and experience, whose responsibilities include, but are not limited to: monitoring project budgets; allocating staff resources; complying with project goals and objectives; evaluating whether the scope of work is being met; serving as official contact for the client, collaborators, and contractors; preparing project progress reports to deliver to the client on a routine basis; and assuming final responsibility for assuring that all project work is completed accurately, on time, and within budget.

Acronym	Term	Definition
PIO	Protocol Information Office	The central office for all protocol-related information management for DCP sponsored trials. The mission of the PIO is to coordinate all administrative aspects related to clinical trial development to assure that quality protocols are developed in the most expeditious and efficient manner possible. Towards that end, the PIO collects, processes, tracks, and monitors all protocol-related information between DCP, the study site staff, Westat, and CCS Associates.
PI	Principal Investigator	The individual responsible for the conduct of the study at the clinical center and for ensuring the safety of study participants enrolled at that site (i.e., under whose immediate direction the test agent is administered or dispensed to the study participant). If a team of individuals conducts a trial, the investigator is the responsible leader of the team.
	Project Manager	An appropriately qualified Westat employee, by training or experience, whose responsibilities include, but are not limited to, project goal planning, supervision of staff, and evaluation and assessment of project activities. The project manager's responsibilities may also include conducting on-site monitoring visits.
PK	Pharmacokinetics	The study of bodily absorption, distribution, and metabolism and excretion of compounds and medicines.
	Protocol	A formal written document which states the rationale, objectives, and statistical design of a clinical research trial.
PUCRG		Prostate and Urologic Cancer Research Group, one of the DCP organ system groups.
QA	Quality Assurance	Applies to on-site and institutional systems and processes established to ensure that the trial is performed and the data is generated in compliance with GCP, SOPs, and the protocol.
QOL	Quality of Life	Description of the physical, psychological, and social dimensions of the health status of a subject.
	Randomization	A method used to prevent bias in research. People are assigned by chance, often by computer, either to receive the study agent (intervention group) or not (control group).

Acronym	Term	Definition
RDC/RDE	Remote Data Capture/ Remote Data Entry	Systems for directly entering data from investigational sites electronically rather than by the physical transfer of data on paper CRFs.
SAE	Serious Adverse Event	Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgement, they may jeopardize the participant and may require medical to surgical intervention to prevent one of the outcomes listed in this definition.
	Site Monitor	A Westat employee (or an employee of a subcontractor of Westat) responsible for on-site monitoring of the conduct of a trial at each site to ensure that it is conducted according to protocol specifications, company procedures, and government requirements.
	Site Visit	On-site investigation of the facilities and/or clinical research process at an institution conducting DCP-sponsored clinical research by DCP staff or its representatives.
	Sponsor	An individual company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial, but who does not actually conduct the investigation
SOPs	Standard Operating Procedures	Written procedures describing sponsor, CRO, site or IRB procedures, or systems governing their processes. Also: standard, detailed instructions for managing a clinical trial. SOP documents provide a general framework to provide the means of efficient implementation and performance of all the functions and activities for the trial described in the SOP.
	Study Coordinator	The responsible person at the clinical site who is the primary contact at the site and ensures that the studies are conducted appropriately.
	Subinvestigator	Individuals (research fellow, resident, associates) who assist the PI in the conduct of the clinical trial. A subinvestigator has authority delegated to him or her by the PI
URL	Universal Resource Locator	The complete address of a resource and has everything the system needs to find a document and its server on the web.

Appendix C

Form FDA 1572

APPENDIX C. FORM FDA 1572

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION **STATEMENT OF INVESTIGATOR** ***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*** (See instructions on reverse side.)	Form Approved: OMB No. 0910-0014. Expiration Date: September 30, 2002. *See OMB Statement on Reverse.* NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FORM FDA 1572 (8/01) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

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8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

Appendix D

DCP Protocol Deviation Notification Form

APPENDIX D. PROTOCOL DEVIATION NOTIFICATION

DIVISION OF CANCER PREVENTION

PROTOCOL DEVIATION NOTIFICATION

Patient No.:	Drug Under Investigation:	Study (Indication):
Sponsor: NCI, DCP	IRB Protocol No.:	NCI Contract No:
Investigator:	Site:	
Phone No.:	FAX No.:	

NCI is being notified of the following protocol deviation (describe and include specific criteria and protocol section):

Reason for deviation:

Action to be taken to prevent this from recurrence:

Form completed by PI (print name): _____

PI Signature: _____ Date: _____
month/day/year

Review of protocol deviation by the NCI Monitor and any required action to be taken:

NCI Monitor signature: _____ Date: _____

cc: Protocol File at Westat ; Contract File at CCSA; AND Case Report Form Binder at Site

Revised August 2002

Appendix E

DCP Guidelines and Serious Adverse Event Report Form

Appendix E
Adverse Event Reporting Chart: Summary of Investigator's Obligations for Reporting Adverse Events in Phase I–III Clinical Trials to the National Cancer Institute, Division of Cancer Prevention (DCP)

Reaction	*Reporting Obligation*
a. ALL SERIOUS ADVERSE EVENTS Any adverse event (AE) occurring at any dose that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.	REPORT BY PHONE TO DCP WITHIN 24 HOURS.[1] (written report to follow within 48 hrs[2])
b. ALL ADVERSE EVENTS (SERIOUS, NON-SERIOUS)[3]	REPORTED in the AE CRF and Progress Reports.

[1] Telephone number available 24 hours daily: 301-496-8563 (Recorder after hours); FAX: 301-402-0553 or 301-594-2943.

[2] Report to: **Medical Monitor (as specified in the contract)**
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 201
9000 Rockville Pike
Bethesda, MD 20892
For Express (*e.g.*, Federal Express, DHL, Airborne) or Hand Delivery
Executive Plaza North, Suite 201
6130 Executive Blvd.
Rockville, MD 20852

[3] A list of all known toxicities can be found in the Investigator's Brochure, package insert, or other material provided by NCI.

NCI, DIVISION OF CANCER PREVENTION (DCP)
SERIOUS ADVERSE EVENT FORM

REQUIRED FIELDS ON ALL REPORTS

Today's Date:	Sponsor: NCI, DCP	Study (Indication):
Drug under Investigation:	IND No.:	

A. Study Subject Information

1. Patient Initials	2. Date of Birth: _____ (Month/Day/Year)	3. Weight at Time of Event: _____ [ ] kg [ ] lbs. [ ] not available	4. Height at Time of Event: _____ [ ] cm [ ] ft [ ] not available

B. Event Information

[ ] Initial Event Report [ ] Follow-up	Gender: (circle one) M F	Dose at Event:
Event Onset Date: (Month/Day/Year)	Primary Event (diagnosis):	
Event Approx. Time: (Indicate A.M./P.M.)		
Event Occurred at:		
Duration of Drug Exposure at Event:	Primary Treatment Approx. Time (A.M./P.M.): Primary Treatment of Event:	
Attending Physician (Name): Phone/FAX No.: Hospital/Clinic: Address:		
Describe Event (if applicable, include dates of hospitalization for event):		
Form Completed by: (Print Name) _____ Title_____ Investigator Signature _____ Date _____ (Month/Day/Year) Phone No. _____		

NCI Contract/Grant No._____ Study Subject No._____
IRB Protocol No. _____

ALL FIELDS APPEARING IN THE FOLLOWING PAGES (C–F) MUST BE COMPLETED FOR THE INITIAL REPORT; THEREAFTER, FILL IN ONLY SECTIONS THAT PROVIDE ADDITIONAL/ CORRECTIVE INFORMATION.

C. Site information

1. Investigator Name

2. Address

D. Suspect Medication(s)

1. Study Design: [ ] Blind [ ] Open/Unblind

Possible Dose (*e.g.,* 300 mg) _____ Frequency (*e.g.,* qd) _____ Route (*e.g.*, po)_____

2. Study Drug

Formulation (*e.g.,* tablet, solution)

Lot No. (If known)

3. Start Date of Study Drug (Month/Day/Year):

4. Was blind broken due to event? [ ] No [ ] Yes [ ] NA

5. Was Study Drug stopped/interrupted/reduced in response to event? [ ] No [ ] Yes

>> If yes, complete a–e:

a. If stopped, specify date study drug last taken: _____ [ ] NA
(Month/Day/Year)

b. If reduced, specify: New dose _____ Date reduced _____ [ ] NA
(Month/Day/Year)

c. If interrupted, specify total number of days not given: _____ [ ] NA

d. Did event abate after study drug was stopped or dose reduced? [ ] NA [ ] Yes [ ] No

e. Did event reappear after study drug was reintroduced? [ ] NA [ ] Yes [ ] No

6. Was patient taking any other medications concomitantly at the time of the event? [ ] No [ ] Yes >> If yes, complete below.

(DO NOT LIST DRUGS USED TO TREAT EVENT)

Drug Name Doses (units, frequency, route, indication for use)	Start Date			Stop Date or mark (X) if continuing			
	Month	Day	Year	Month	Day	Year	(X)

(continue on a separate sheet if necessary)

E. Adverse Event

1. Relevant Laboratory/Diagnostic Tests [ ] No tests performed

Date	Test	Results	
		Actual Value	Normal Range
Month Day Year			

(continue on a separate sheet if necessary)

2. Relevant Medical History, including preexisting conditions (*e.g.,* allergies, pregnancy, smoking & alcohol use, hepatic/renal dysfunction, medical/surgical history, *etc.*)

Date (if known) Diseases/Surgeries/Treatment

(continue on a separate sheet if necessary)

3. **NCI Toxicity GRADE of the Event** (use NCI Common Toxicity Criteria): [ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4
If not gradable by NCI CTC, check one of the following: [ ] Mild (Causing no limitation of usual activities)
[ ] Moderate (Causing some limitation of usual activities) [ ] Severe (Causing inability to carry out usual activities)

4. Why Serious?
[ ] Results in death [ ] Is life-threatening [ ] Requires inpatient hospitalization or prolongation of existing hospitalization
[ ] Results in persistent or significant disability/incapacity [ ] Is a congenital anomaly/birth defect
[ ] Other, specify:_____

5. Outcome of Event (at time of report)

[ ] Resolved–date: _____ [ ] Improved [ ] Unchanged [ ] Worse [ ] Not available
(Month/Day/Year)
[ ] Fatal–date of death: _____ Autopsy performed? Y N
(Month/Day/Year) (circle one)
Cause of death: _____ (please attach death certificate and autopsy report, if applicable)

6. Investigator's opinion of the relationship between the event and the study drug (If more than one event is being reported, list secondary events and corresponding relationship to study drug in the comments section below.) Check applicable box:

[ ] Not related [ ] Unlikely [ ] Possible [ ] Probable [ ] Definite

7. Was this event reported by the Investigator to (check all that apply): [ ] IRB [ ] Manufacturer/Distributor
[ ] Other Investigators participating in this study, if checked, please list names and institutions

_____
_____
_____
_____

F. Comments/Clarifications:

FOR NCI USE ONLY

1. Date NCI notified of event (Month/Day/Year):

2. Medical Monitor Review:

   Medical Assessment of Event (including drug relationship and expectancy):

Is this an FDA reportable (7 calendar days) event? [ ] Yes [ ] No

Is this an FDA reportable (15 calendar days) event? [ ] Yes [ ] No

>> If No, specify reason:_____

Is more information expected? [ ] Yes [ ] No

>> If Yes, specify:_____

Is this event to be communicated to other NCI contractors using this investigational drug? [ ] Yes [ ] No

>> If Yes, how? By telephone (attach a TC Form): [ ] Yes, attached TC Form [ ] No

Other (FAX, mail, e-mail, *etc.*): [ ] Yes, attached a copy of the correspondence [ ] No

Medical Monitor: Print name _____ Signature _____ Date _____

Appendix F

Initiation Visit Report Forms

APPENDIX F. INITIATION VISIT REPORT FORMS

DCP PROJECT
CLINICAL SITE INITIATION VISIT REPORT

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

Document Number:

Date(s) of Visit:

Conducted by:

Clinical Site Personnel Involved with the Study:

NAME	TITLE	MET WITH CRA MONITOR (Y/N)	PRESENT AT DEBRIEFING (Y/N)
	Principal Investigator		
	Study Coordinator		
	Pharmacist		
	Other		

Additional Comments:

CLINICAL SITE MONITORING
INITIATION VISIT CHECKLIST

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Background and Purpose of Study				
Study Objectives and Design				
Study Procedures				
Clinical Evaluations				
Laboratory Evaluations				
Schedule of Evaluations				
Specimen Collection, Processing, Storage, and Shipping				
Missed Evaluations				
Protocol Deviations/Violations				
Ordering of Supplies				
Protocol Initiation and Enrollment				
Informed Consent Process				
Timing of Pre-Entry Period				
Exemptions				
Randomization or Enrollment				
Adverse Experience Reporting				
AER Guidelines				
Procedures and Forms				
Toxicity Management				
Receipt, Review, and File Investigator's Brochures				
Receipt, Review, and File Package Inserts				
Receipt, Review, and File Safety Reports				
Endpoints and Treatment Discontinuation				
Required Evaluations				
Data Collection				
Procedures				
CRF Completion Guidelines				
Common Errors				
Corrections				
Form Update Procedures				
Missed Visits				
Data Inquiries				
Disposition of Forms				
Source Documentation				

CLINICAL SITE MONITORING
INITIATION VISIT CHECKLIST (continued)

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Data Collection (continued)				
What Is Acceptable				
Shadow Files				
Case Report Forms as Source Documents				
Document Retention				
Policy and Procedure Manuals				
Westat Procedures Handbook				
Other (list under comments)				
Regulatory Documentation				
Protocol Signature Page				
IRB/IEC Documentation				
IRB/IEC - Approval Letter				
IRB/IEC-Approved Informed Consent Form				
IRB/IEC-Approved Advertisements				
IRB/IEC-Approved Participant Information Sheets				
Annual Renewal				
Amendments				
IRB/IEC Roster				
Assurance Number				
Laboratory Certification				
Laboratory Normal Ranges				
Documentation of IRB/IEC submission of Investigator's Brochures				
Documentation of IRB/IEC submission of Package Inserts				
Documentation of IRB/IEC submission of Safety Reports				
Letter of Understanding or Confidentiality Agreement				
Documentation of Dangerous Goods Training				
Documentation of Human Participants Protection Training				

CLINICAL SITE MONITORING
INITIATION VISIT CHECKLIST (continued)

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Recordkeeping Requirements				
Participant Screening Log				
Participant Identification Logbook				
Master Signature Log				
Site Visit Log				
Original Signed Informed Consent Forms				
Source Documents/Confidentiality				
Study-related Correspondence				
Telephone Log				
Laboratory Procedures				
Specimen Storage and Disposition				
Shipping Procedures				
Specimen Shipping Log				
Pharmacy				
Dissemination of Information to the Pharmacist				
Drug Storage & Accountability				
Pharmacy Guidelines				
Current Protocol Versions				
Documentation of Informed Consents				
Investigator's Brochures				
Safety Reports				
Communication				
Quality Assurance Plan				
Quality Assurance (QA) Procedures				
Review QA Plan				
Maintain QA Log				
Expected Performance Parameters				
Communication				
With Westat Personnel				
With Protocol Team				
Study Management				
Budget Management and Invoicing				
Site Monitoring				
Purpose				
Frequency				
Reports				

Prepared by: Date:

(Signature)

Appendix G

Annual Visit Report Forms

APPENDIX G. ANNUAL VISIT REPORT FORMS

DCP PROJECT
PRELIMINARY REPORT OF AUDIT FINDINGS

Name of Clinical Site:	Date(s) of Site Visit:
Principal Investigator:	Westat Team Monitor:
Document Number:	DCP Representative(s) Present:

Instructions: For the following categories, indicate the final assessment for each of the three components of the monitoring visit.

1. Assessing the IRB and Informed Consent Findings:

_____ **Acceptable:** No deficiencies identified.
Few minor deficiencies identified.
Major deficiencies identified during the site visit that were addressed and/or corrected prior to the site visit for which documentation exists and no further action is required.

_____ **Acceptable, Follow-up:** Multiple minor deficiencies identified.
Major deficiencies identified during the site visit, but not corrected and/or addressed prior to the site visit.

_____ **Unacceptable:** Multiple major deficiencies identified.
A single major flagrant deficiency found.
Excessive numbers of minor deficiencies found.

2. Assessing the Accountability of Investigational Agents and Pharmacy Operations:

_____ **Acceptable:** Compliance found for security, drug accountability record forms completed correctly, protocol and drug-specific usage and/or return of study drug in DCP repository.
Non-compliant items identified during the site visit that were addressed and/or corrected prior to the site visit for which documentation exists and no further action is required.

_____ **Acceptable, Follow-up:** Category found non-compliant during the site visit which was not corrected and/or addressed prior to the site visit.

_____ **Unacceptable:** Inability to track the disposition of NCI/DCP supplied investigational **agents**
Multiple non-compliant categories identified.

3. Review of Patient Records:

_____ **Acceptable:** No deficiencies identified
Few minor deficiencies identified.
Major deficiencies identified during the site visit that were addressed and/or corrected prior to the site visit for which documentation exists and no further action is required.

_____ **Acceptable, Follow-up:** Multiple minor deficiencies identified.
Major deficiencies identified during the site visit, but not corrected and/or addressed prior to the site visit.

_____ **Unacceptable:** Multiple major deficiencies identified.
A single major flagrant deficiency found.
Multiple minor deficiencies of a recurring nature found in a majority of the patient cases reviewed.

DCP PROJECT

CLINICAL SITE ANNUAL VISIT REPORT

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

Contract Number:

Date(s) of Visit:

Conducted by:

Clinical Site Personnel Involved with the Study:

NAME	TITLE	PRESENT AT DEBRIEFING (Y/N)
	Principal Investigator	
	Study Coordinator	
	Pharmacist	
	Other	

Additional Comments:

II. REGULATORY REVIEW

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No, "N/A" = Not applicable). Please provide comments whenever necessary or helpful.

DOCUMENTS AND STORAGE	Y	N	N/A	COMMENTS
1. Copy of the protocol and all pertinent amendments on file				
2. Initial IRB/IEC approval of protocol				
3. IRB/IEC approval of most recent protocol amendments				
4. Annual IRB/IEC renewal of protocol				
5. IRB/-approved consent form and all form revisions on file				
6. Adverse Event Safety reports submitted to IRB/IEC				
7. Serious Adverse Event reports submitted to CCSA				
8. Copy of one of the following IRB/IEC compliance documents: IRB/IEC roster, DHHS #, or Assurance #				
9. Research records stored in a secure area				
10. Form FDA 1572 current				
11. Laboratory certification up-to-date				
12. Copy of normal range values for each laboratory used				
13. Investigator's Brochure(s) on file and securely stored				
14. Site Monitoring Visit log up-to-date				
15. Site Personnel Signature log up-to-date				

Additional comments:

III. RECORD REVIEW AND SUMMARY

Instructions: Write the patient identification number for each chart reviewed in column one. Record the visit week to be begin review for a specific patient in the second column. Record the last visit reviewed for the specific patient in the third column. In the summary table, provide the requested information for each of the items listed ("Y" = Yes, "N" = No). Please provide comments whenever helpful or necessary.

Total # of Charts Reviewed: _____

SUBJECTS REVIEWED (ID #)	BEGAN REVIEW (AT WEEK)	TO VISIT (INCLUSIVE)

SUMMARY OF FINDINGS FOR SITE MONITORED CASES	Y	N	COMMENTS
1. 100% of informed consents appropriately obtained and documented.			As of :____/____/____
2. Participant eligibility verified.			
3. Source documentation adequate.			
4. Adverse events (including SAEs) appropriately documented and reported.			
5. Endpoints correctly reported.			
6. Clinical events (i.e., change in patient status, concurrent illness) and concomitant meds recorded on CRFs.			
7. Clinical and laboratory evaluations obtained as per protocol.			
8. Laboratory samples correctly collected and shipped/stored/evaluated.			
9. Source documents and CRFs indicate compliance with protocol treatment and blinding procedure, if applicable.			
10. Major deficiencies noted and reported as needed.			

Additional comments:

IV. SITE OPERATIONS ASSESSMENT

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No, "N/A" = Not applicable). Please provide comments whenever necessary or helpful.

ITEMS EVALUATED	Y	N	N/A	COMMENTS
1. Adequate resources (e.g., facilities, staffing)				
2. Internal quality assurance activities				
3. Participant accrual and retention				

Additional comments:

I. <u>STATUS OF PAST FINDINGS</u>: (Have corrections been made to errors which were identified previously?)

VII. <u>DISCUSSION OF CURRENT FINDINGS WITH STAFF</u>: (Include problems identified, if any, and recommendations/action items for corrections.)

VIII. <u>ADDITIONAL COMMENTS</u>:

Prepared by: Date:

(Signature)

Appendix H

Close-out Visit Report Forms

APPENDIX H. CLOSE-OUT VISIT REPORT FORMS

DCP PROJECT
CLINICAL SITE CLOSE-OUT VISIT REPORT

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

Contract Number:

Date(s) of Visit:

Conducted by:

Clinical Site Personnel Involved with the Study:

NAME	TITLE	AVAILABLE DURING DISCUSSIONS (Y/N)
	Principal Investigator	
	Study Coordinator	
	Pharmacist	
	Other	

Additional Comments:

II. CLOSE-OUT REVIEW

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No). Please provide comments whenever necessary or helpful.

OBJECTIVE	Y	N	COMMENTS
1. Ensure that all case report forms for each subject have been completed.			
2. Verify that all data have been keyed on-site or all forms have been submitted to the coordinating center. If they have not, discuss the timeline for accomplishing this and document in the comments.			
3. Review the status of all outstanding data edits, queries, or delinquent forms and timeline for their resolution.			
4. Verify that a signed, informed consent is on file for each study participant.			
5. Confirm that the IRB/IEC has been informed of the study closure			
6. Verify that all regulatory and other pertinent documents for the protocol (IRB approvals, consent documents, etc.) are up to date and on file.			
7. Ensure that a progress note is included in each participant's medical record indicating that study participant has ended.			
8. Verify that the investigator has plans to submit the final report to DCP, and that a deadline for completion has been identified.			
9. Ensure that the Principal Investigator understands the requirements for reporting of adverse events for subjects who have completed study.			
10. Ensure that the Principal Investigator and study coordinator have received and understand the requirements for retention of study records.			
11. Ensure that study drug has been returned to the repository.			
12. Ensure that all participant specimens have been shipped according to client specifications.			
13. Ensure that all required Drug Accountability has been reconciled and forms have been completed appropriately.			
14. Determine the disposition of participant specimens, including plans for future shipments or period of time they will be stored onsite.			

CLOSE-OUT REVIEW (continued)

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No). Please provide comments whenever necessary or helpful.

OBJECTIVE	Y	N	COMMENTS
15. If blinded study drug was used, confirm that the tear-off labels were not opened. For any that were opened, documentation should be obtained noting the reason for unblinding.			
16. Ensure that all unused study drug is returned to the client.			

Additional comments:

Prepared by: Date:

(Signature)

Appendix I

Pharmacy Audit

APPENDIX I. PHARMACY AUDIT REPORT

DCP PROJECT
PHARMACY AUDIT REPORT

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

Document Number:

Name and Address of Pharmacy:

Date of Audit:

Conducted by:

Investigational Pharmacy Personnel:

NAME	TITLE	MET WITH MONITOR (Y/N)
	Pharmacist of Record	
	Other Staff / Title	

Additional Comments:

II. MAINTENANCE OF RECORDS

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No). Please provide comments whenever necessary or helpful.

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
A. Are the following protocol-specific documents present?				
1. Form FDA 1572				
2. Prescriber signature list				
3. Most recent version of the protocol for which the site has IRB approval				
4. Participant study assignment list				
5. Drug ordering instructions				
B. Are the following records accessible only to the site pharmacist or his/her designee?				
1. Study assignment lists				
2. Investigational agent accountability/ inventory records				
3. Order forms/shipping receipts				
4. Participant-specific profiles, if used				

III. SECURITY AND STORAGE OF THE INVESTIGATIONAL DRUGS

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
A. Inspect the investigational drug storage area.				
1. Are the investigational drugs stored according to the manufacturer's specifications?				
2. Are supplies sufficient?				
3. Outdated drugs are not stored together with the active drug supply.				
4. Is refrigerator and/or freezer storage available?				
a. If yes, describe location of refrigerator and/or freezer and method of monitoring temperature.				
5. Is study drug stored in a secure, limited access area?				

IV. DRUG ACCOUNTABILITY, PREPARATION AND DISPENSATION

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
A. Accountability				
1. Do the increases in drug inventory on the investigational accountability records agree with the shipment receipts?				
2. Are the accountability records legible and complete with each entry initialed by the pharmacists of record or other authorized personnel?				
3. Are there any entries in the accountability records that indicate dispensing of investigational agents to persons other than participants enrolled in this/these studies?				
4. If study drug is commercially available, are procedures in place to assure that study drug is not stored together with the general supply?				
5. Does the inventory balance documented on the accountability record correspond precisely with the actual physical inventory?				
a. If No, provide actual numbers of the agent counted as well as the amount recorded on the accountability record for each discrepancy noted				

Drug	Accountability Record	Inventory Amount

Explanation/Discussion				
6. Is the amount of drug supply on hand reasonable based on current enrollment and accrual rate?				

IV. DRUG ACCOUNTABILITY, PREPARATION AND DISPENSATION (continued)

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
B. Drug Preparation and Dispensing				
1. Describe the routine procedure for dispensing study drugs.				
a. When, in relation to the participant study visit, is the study drug prepared? Describe:				
b. How does the investigational pharmacist usually receive study drug prescriptions? Describe:				
c. To whom does the investigational pharmacist dispense study drugs? Describe:				

Additional Comments:

Prepared by: Date:

(Signature)

Appendix J

Essential Documents for the Conduct of a Clinical Trial

APPENDIX J.
ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

Essential documents are those documents that individually and collectively evaluate the conduct of a trial and the quality of the data produced. These documents demonstrate the compliance of the investigator and sponsor with the standards of Good Clinical Practice (GCP) and all applicable regulatory requirements. Note: The ICH Guidelines have been adopted by the FDA as guidances, not regulations.

The Office of Human Research Protection (OHRP) and Health and Human Services (HHS) regulations (45 CFR 46) and Good Clinical Practice recommendations apply for all trials that receive funding from a Health and Human Service agency. Trials with a Food and Drug Administration (FDA) Investigational Drug Application (IND) must additionally comply with 21CFR regulations.

Document	Purpose	File	Regulation/Reference
Assurance Number	The institution is responsible for obtaining and maintaining a current Health and Human Services (HHS) Assurance Number through the Office of Human Research Protection (OHRP) ▪ The PI is responsible for ensuring that a current Assurance Number is in effect while conducting research on human subjects ▪ All performance sites must maintain the Assurance Number on file and obtain renewal prior to expiration	In a regulatory binder at the site A copy of the Assurance Number must be on file with the sponsor	**45 CFR 46**
Auditing Reports	1. Document audit visits and findings of the auditor 2. Copies of all audit visit reports are filed at the site and sent to the sponsor	In the regulatory binder at the site	**ICH Guidance: E6 Good Clinical Practice: Section 5.19.3**
Case Report Form	1. Signed, dated, and completed Case Report Forms (CRFs): ▪ Document that the investigator or authorized member of the investigator's staff confirms the observations recorded ▪ Document all changes/additions or corrections made to CRF after initial data were recorded 2. Site retains copy 3. Originals retained by sponsor after study completion and/or site closure	In the patient's research record at the site	**21 CFR 312** **ICH Guidance: E6 Good Clinical Practice: Sections 8.3.14 8.3.15**
Communications	1. Document all relevant communications other than site visits, for example: ▪ Letters ▪ Meeting Notes ▪ Notes of Telephone Calls ▪ E-Mail Messages	In the appropriate regulatory binder or patient's	**ICH Guidance: E6 Good Clinical Practice: Section 8.3.11**

Document	Purpose	File	Regulation/Reference
Communications (continued)	2. Subject specific communications must be filed with source documents in the subject's research record 3. Document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting, etc. 4. Save electronic media, originals, and/or certified copies	research record at the site	
Consent Form	1. Obtain signed informed consent forms in accordance with the protocol. They must be dated prior to participation of each subject in a trial 2. Save all versions submitted and approved by site's institutional review board (IRB) 3. Document revisions of the trial-related documents that take effect during the trial; save any revisions to: ▪ Informed Consent ▪ Any other written information provided to the subjects 4. Retain consents obtained for screening purposes even if the subject was not enrolled in the study 5. Non-English speaking subjects must be consented in a language they can understand Note: Annual Review and/or changes in consent forms due to AEs and/or Safety Memos are at the directive of the site's IRB	IRB approved copies in the regulatory binder at the site and signed consents in the patient's research record or in the regulatory binder at the site	**45 CFR 46** **21 CFR 50** **21 CFR 56** **ICH Guidance: E6 Good Clinical Practice: Sections** **8.3.12** **8.2.3** **8. 3.2**
Curriculum Vitae	1. Document the qualifications and eligibility of the investigator(s) subinvestigator(s), and other key personnel to conduct a trial and/or to provide medical supervision of subjects 2. Available for all investigators, subinvestigators, any other person listed on FDA 1572 Form, and other key personnel at the site 3. Submit updated/revised investigator(s) and subinvestigator(s) CV to the PIO	In the regulatory binder at the site	**ICH Guidance: E6 Good Clinical Practice: Sections** **8.2.10** **8.3.5**
FDA 1572 Form	1. Document that the Investigator of Record (IoR) agrees to conduct the trial according to the obligations stated in the form 2. Update as study personnel and/or other data on the form changes 3. The original version and any updated forms must be retained as per regulatory requirements 4. The Investigator in box 1 of FDA 1572 Form is the individual who must sign and date the signature box 5. Only laboratories specified in the protocol need to be listed in Section 4	In the regulatory binder at the site	**21 CFR 312**

Document	Purpose	File	Regulation/Reference
FDA 1572 Form (continued)	6. Section 6 must list any individual: ▪ Responsible for conducting/ performing study visits ▪ Authorized to prescribe study medication This may include but is not limited to the following: ▪ MDs ▪ Pharmacist of Record ▪ Nurse Practitioner ▪ Physician's Assistant ▪ Study Coordinator ▪ Research Nurse If there are no individuals that need to be listed, then write "NONE"		
Final Close Out Monitoring Report	Final report by investigator is sent to the IRB where required and, where applicable, to the regulatory authorities, to document completion of the trial. Included is the following information: ▪ Disposition of the subjects ▪ Location of the research records ▪ Disposition of the specimens ▪ Disposition of the study drugs ▪ Other information as required by the institution or local IRB (e.g., number of patients screened, number enrolled, serious adverse experiences)	In the regulatory binder at the site	**ICH Guidance: E6 Good Clinical Practice: Sections 4.13 8.4.5 8.4.7**
Financial Disclosure	1. Document the financial aspects of the trial and the financial agreement between the investigator/institution and the sponsor for the trial 2. Certification or disclosure statement to: ▪ Certify that there is no financial interest or ▪ Disclose specific financial interests of Investigators and subinvestigators listed on FDA Form 1572, as well as their spouses and dependent children 3. Local institution/IRB and/or Group SOPs may have additional requirements	In the regulatory binder at the site	**ICH Guidance: E6 Good Clinical Practice: Section 8.2.4**
Investigational Drug Brochures (IDBs) and Safety Package Inserts	1. Document that relevant and current scientific information about the investigational product has been provided to the investigator 2. Include updates to document that investigator is informed in a timely manner of relevant information as it becomes available 3. Keep a copy on file for EACH study medication used within the protocol 4. Include the following: ▪ The most recent version ▪ Addendum to IDBs ▪ Safety letters 5. Some IDBs must be shredded per protocol/sponsor. Some studies require that a historical trail of IDBs and their individual IRB letters of acknowledgement be retained	In the regulatory binder at the site and in the pharmacy	**ICH Guidance: E6 Good Clinical Practice: Sections 8.2.1 8.3.1**

Document	Purpose	File	Regulation/Reference
Investigational Product/Study Drug Accountability	1. The Pharmacist of Record must keep records to account for the disposition of investigational products/study drugs by documenting the following: ▪ Shipment dates ▪ Batch number 2. Document tracking of: ▪ Product batch ▪ Review of shipping conditions ▪ Accountability 3. Document that the investigational products have been used according to the protocol 4. Document the final accounting of investigational products: ▪ Received at the site ▪ Dispensed to subjects ▪ Returned by the subjects ▪ Returned to the sponsor ▪ Destroyed by the site	In the pharmacy records at the site	**ICH Guidance: E6 Good Clinical Practice: Sections 8.2.15 8.3.8 8.3.23 8.4.1**
IRB Correspondence	1. Copies of all materials submitted to the IRB with dated proof of submission and IRB approval (when appropriate) for the following: ▪ Advertisements: document that recruitment measures are appropriate and not coercive ▪ All versions of consent forms ▪ All protocols and amendments ▪ Annual reports to the IRB ▪ IND safety reports/Adverse Event Report ▪ Initial protocol submission ▪ Investigational drug brochure or safety package inserts ▪ Protocol specific education material ▪ Subject compensation ▪ Any other documents receiving IRB approval or their favorable opinion ▪ Any other written information to be provided to subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent ▪ Any other pertinent communications with the IRB	In the regulatory binder at the site	**45 CFR 46 21 CFR 50 21 CFR 56** **ICH Guidance: E6 Good Clinical Practice: Sections 3.1.4 4.10 5.17.3 8.2.3 8.2.7 8.3.2 8.3.3 8.3.19**

Document	Purpose	File	Regulation/Reference
IRB Membership List	1. Document that composition of IRB/independent ethics committee (IEC) is in agreement with Good Clinical Practice (GCP) 2. Update when members change and as required by local institution/IRB policy 3. Investigator needs current IRB composition on files: ▪ Titles ▪ Affiliation ▪ Names are not necessary	In the regulatory binder at the site	**45 CFR 46** **21 CFR 50** **21 CFR 56** **ICH Guidance:** **E6 Good Clinical Practice:** **Section** **8.2.8**
Laboratory	1. Document competence of facility to perform required tests, and support reliability of results of medical/laboratory/technical procedures/tests: ▪ Certification or Accreditation ▪ Update when certifications expire or laboratory changes to document that tests remain adequate throughout the trial period ▪ Established quality control and/or external quality assessment 2. Document normal values/ranges for medical/laboratory/technical procedures/tests included in the protocol 3. Update documentation of normal values/ranges when they are revised during the trial 4. The reference ranges and certifications must be on file for the following listings: ▪ Local or central laboratories that analyze specimens for the study ▪ Any group central laboratory	In the regulatory binder at the site	**ICH Guidance:** **E6 Good Clinical Practice:** **Sections** **8.2.11** **8.2.12** **8.3.6** **8.3.7**
Screening and Enrollment Randomization Logs	1. Document identification of subjects who entered pretrial screening 2. Document chronological enrollment of subjects by number 3. Screening and enrollment/ randomization logs may be separate or combined 4. Include the following information: ▪ Initials of all patients screened for each study ▪ PID number ▪ Date screened ▪ Date randomized ▪ If not randomized, indicate reason	In the screening files or protocol files at the site	**ICH Guidance:** **E6 Good Clinical Practice:** **Sections** **8.3.21** **8.4.3**
Subject Identification Code List	1. Document that the investigator keeps a confidential list of names of all subjects allocated to trial numbers upon enrolling in a trial 2. Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow up is required 3. List needs to be kept in a confidential manner and for agreed upon time	In the protocol file at site	**ICH Guidance:** **E6 Good Clinical Practice:** **Sections** **8.3.21** **8.4.3**
Serious Adverse Events (SAE)	1. Notification by originating investigator to sponsor of serious adverse events, related reports, and other safety information 2. Notification by sponsor to investigators of safety information	In regulatory file at site	**45 CFR 46** **21 CFR 50** **21 CFR 56**

Document	Purpose	File	Regulation/Reference
Serious Adverse Events (SAE) (continued)	3. Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB of unexpected serious adverse drug reactions and of other safety information		**21 CFR 312** **ICH Guidance: E6 Good Clinical Practice: Sections 4.11 5.16.2 5.17 8.3.16 8.3.17 8.3.18**
Signature Log	1. Document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. Include all site staff working on a study, such as: ▪ Clinicians ▪ Physicians ▪ Pharmacists ▪ Data Personnel 2. Include on the log: ▪ Initials ▪ Legal signature, including first and last name ▪ Printed signature ▪ Credentials (if appropriate)	In the regulatory file at the site	**ICH Guidance: E6 Good Clinical Practice: Section 8.3.24**
Source Documents	1. Document the existence of the subject and substantiate integrity of trial data collected 2. Original documents and/or certified copies of documents related to the trial, medical treatment, and history of the subject 3. Must be signed and dated	As per requirements of local institutions	**21 CFR 11** **21 CFR 312** **ICH Guidance: E6 Good Clinical Practice: Section 8.3.13**
Unblinding	1. Decoding procedures for blinded trials to document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatments 2. Document any decoding that may have occurred at the site during the trial	In the protocol files at the site or in the pharmacy files and in the patient record	**ICH Guidance: E6 Good Clinical Practice: Sections 8.2.17 8.4.6**